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TRANSACTIONS

ASSOCIATION OF AMERICAN PHYSICIANS

THIRTY-FIFTH SESSION

HELD AT ATLANTIC CITY, N. J.

MAY 4 AND 5, 1920

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1920

NOTICE

The Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

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JAN
1922

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ALTERNATE REPRESENTATIVE

FRANCIS W. PEABODY, M.D.

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REPRESENTATIVE ON THE EXECUTIVE COMMITTEE OF THE CONGRESS OF AMERICAN PHYSICIANS AND SURGEONS

FRANCIS W. PEABODY, M.D.

ALTERNATE REPRESENTATIVE

G. CANBY ROBINSON, M.D.

OFFICERS OF THE ASSOCIATION

FROM ITS ORGANIZATION TO THE PRESENT TIME

Year.	*President.*	*Vice-President.*	*Recorder.*	*Secretary.*	*Treasurer.*
1886.	Francis A. Delafield	.....	.....	James Tyson.	A. B. Ball.
1887.	S. Weir Mitchell.	Francis Minot. R. Palmer Howard.	J. T. Whittaker.	G. L. Peabody.	W. W. Johnston.
1888.	Wm. H. Draper.	Francis Minot. R. Palmer Howard.	William Osler.	Henry Hun.	W. W. Johnston.
1889.	Francis Minot.	R. Palmer Howard. S. C. Busey.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1890.	S. C. Busey.	William Pepper. Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1891.	Wm. Pepper.	Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1892.	Henry M. Lyman.	George Ross.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1893.	A. L. Loomis.	Reginald H. Fitz.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1894.	Reginald H. Fitz.	William Osler.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1895.	Wm. Osler.	A. Jacobi.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1896.	A. Jacobi.	J. M. Da Costa.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1897.	J. M. Da Costa.	F. C. Shattuck.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1898.	F. C. Shattuck.	G. Baumgarten.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1899.	G. Baumgarten.	E. G. Janeway.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1900.	E. G. Janeway.	Wm. H. Welch.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1901.	Wm. H. Welch.	H. P. Walcott.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1902.	James C. Wilson.	Jas. Stewart.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1903.	James Stewart.	W. T. Councilman.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1904.	W. T. Councilman.	E. L. Trudeau.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1905.	E. L. Trudeau.	Frank Billings.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1906.	Frank Billings.	F. P. Kinnicutt.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1907.	F. P. Kinnicutt.	James Tyson.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1908.	James Tyson.	V. C. Vaughan.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1909.	V. C. Vaughan.	Henry Hun.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1910.	Henry Hun.	F. Forchheimer.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1911.	F. Forchheimer.	J. George Adami.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1912.	J. George Adami.	L. F. Barker.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1913.	L. F. Barker.	Simon Flexner.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1914.	Simon Flexner.	S. J. Meltzer.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1915.	S. J. Meltzer.	Henry Sewall.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1916.	Henry Sewall.	George Dock.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1917.	George Dock.	F. H. Williams.	T. R. Boggs.	T. McCrae.	J. P. C. Griffith.
1918.	F. H. Williams.	Alex. McPhedran.	T. R. Boggs.	T. McCrae.	Joseph A. Capps.
1919.	Alex. McPhedran.	Herman M. Biggs.	W. W. Ford.	T. McCrae.	Joseph A. Capps.
1920.	H. M. Biggs.	W. S. Thayer.	T. R. Boggs.	T. McCrae.	Joseph A. Capps.
1921.	W. S. Thayer.	H. C. Moffitt.	T. R. Boggs.	T. McCrae.	Joseph A. Capps.

ACTIVE MEMBERS

ELECTED

1892. Abbott, Alexander C., Laboratory of Hygiene, University of Pennsylvania, Philadelphia.
1896. Abel, John J., Johns Hopkins Medical School, Baltimore, Md.
1894. Adami, J. George, Univ. of Liverpool, Liverpool, England.
1905. Adams, Samuel S., 1801 Connecticut Ave., Washington, D. C.
1919. Addis, Thomas, Lane Hospital, San Francisco.
1918. Allen, F. M., Rockefeller Institute, 66th St. and Ave. A., New York.
1911. Anders, James M., 1605 Walnut St., Philadelphia.
1913. Anderson, John F., 195 College Ave., New Brunswick, N. J.
1911. Ashford, Bailey K., U. S. Army, San Juan, P. R.
1913. Auer, John, Rockefeller Institute, 66th St. and Ave. A, New York.
1919. Austin, J. H., Rockefeller Institute, 66th St. and Ave. A, New York.
1899. Barker, L. F., 1035 North Calvert St., Baltimore, Maryland.
1916. Bass, Charles C., Tulane Univ., New Orleans.
1894. Biggs, Herman M., 5 West 58th St., New York.
1895. Billings, Frank, 1550 North State Parkway, Chicago.
1901. Blumer, George, 204 York St., New Haven, Conn.
1913. Boggs, Thomas R., 21 West Chase St., Baltimore, Md.
1890. Bond, Charles S., 112 North 10th St., Richmond, Ind.
1915. Brill, Nathan E., 48 W. 76th St., New York.
1913. Brooks, Harlow, 47 West 9th St., New York.
1911. Brown, Lawrason, 104 Main St., Saranac Lake, N. Y.
1904. Brown, Philip K., 516 Sutter St., San Francisco, Cal.
1914. Brown, Thomas R., 19 W. Biddle St., Baltimore.
1918. Brown, W. H., Rockefeller Institute, 66th St. and Ave. A, New York.
1913. Bunting, C. H., University of Wisconsin, Madison.
1899. Cabot, R. C., 1 Marlborough St., Boston.
1912. Camac, C. N. B., 128 E. 60th St., New York.
1914. Cannon, Walter B., Harvard Medical School, Boston.
1908. Capps, Joseph A., 150 Michigan Ave., Chicago.
1919. Carter, E. P., 204 Stratford Road, Guilford, Baltimore.

ELECTED

1907. Christian, Henry A., 721 Huntingdon Ave., Boston.
1898. Cohen, Solomon Solis, 1525 Walnut St., Philadelphia.
1917. Cohn, Alfred E., 315 Central Park West, New York.
1909. Cole, Rufus I., 960 Park Ave., New York.
1914. Coleman, Warren, 58 West 55th St., New York.
1904. Collins, Joseph, 37 West 54th St., New York.
1908. Conner, Lewis A., 121 East 62d St., New York.
1906. Coplin, W. M. L., 606 South 48th St., Philadelphia.
1917. Dochez, Alphonse R., Rockefeller Institute, 66th St. and Ave. A, New York.
1893. Dock, George, 600 S. Kingshighway, St. Louis, Missouri.
1920. Draper, G., 116 East 63d St., New York.
1904. Edsall, David L., 80 Marlborough St., Boston, Mass.
1920. Elliott, C. A., 30 North Michigan Ave., Chicago.
1915. Emerson, Charles P., Medical School, University of Indiana, Indianapolis.
1918. Emerson, Haven, 120 E. 62d St., New York.
1915. Erlanger, Joseph, 600 S. Kingshighway, St. Louis.
1900. Ewing, James, 260 West 57th St., New York.
1920. Eyster, J. H., Univ. of Wisconsin, Madison, Wis.
1904. Finley, Frederick G., 1013 Dorchester St., Montreal, Canada.
1895. Flexner, Simon, Rockefeller Institute for Medical Research, 66th Street and Avenue A, New York.
1913. Ford, W. W., 1134 Cathedral St., Baltimore, Md.
1916. Foster, Nellis B., 121 East 62d St., New York.
1908. Freeman, R. G., 211 W. 57th St., New York.
1913. Friedenwald, Julius, 1013 N. Charles St., Baltimore, Md.
1917. Frothingham, Jr., Channing, 395 Marlborough St., Boston.
1918. Fulton, F. T., 273 Bowen St., Providence, R. I.
1894. Fussell, M. Howard, 421 Lyceum Ave., Manayunk, Phila.
1903. Futcher, Thomas B., 1129 North Calvert St., Baltimore, Md.
1914. Gay, Frederick P., University of California, Berkeley.
1904. Gordinier, H. C., 89 4th St., Troy, N. Y.
1901. Greene, Charles L., 150 Lowry Arcade, St. Paul.
1890. Griffith, J. P. Crozer, 1810 Spruce St., Philadelphia.
1919. Hamburger, W. W., 104 S. Michigan Ave., Chicago.
1908. Hamilton, W. F., 287 Mountain St., Montreal, Canada.
1915. Hamman, Louis V., 714 Park Ave., Baltimore.
1890. Hare, Hobart A., 1801 Spruce St., Philadelphia.
1918. Hart, T. S., 160 W. 59th St., New York.
1918. Heard, J. D., 6101 Penn Ave., Pittsburgh, Pa.
1898. Herrick, James B., People's Gas Building, Chicago.
1920. Hess, A. F., 16 West 86th St., New York.

ELECTED

1910. Hewlett, Albion W., Stanford Med. School, San Francisco, Cal.
1911. Hoover, C. F., Lakeside Hospital, Cleveland, Ohio.
1914. Howard, Campbell P., Iowa City, Iowa.
1911. Howard, W. T., 1213 N. Calvert St., Baltimore.
1911. Howland, John, Johns Hopkins Hospital, Baltimore, Md.
1916. Hunt, J. Ramsay, 20 W. 50th St., New York.
1907. Hunt, Reid, Harvard Med. School, Boston.
1917. Irons, Ernest E., 122 S. Michigan Ave., Chicago.
1901. Jackson, Henry, 380 Marlborough St., Boston.
1916. Jobling, James W., Dept. of Pathology, Columbia Univ., New York.
1902. Joslin, E. P., 81 Bay State Road, Boston.
1916. Karsner, Howard T., Lakeside Hospital, Cleveland.
1915. Klotz, Oskar, Rockefeller Foundation, 61 Broadway, New York.
1900. Koplik, Henry, 30 East 62d St., New York.
1920. Krause, A. K., The Hopkins Hospital, Baltimore.
1920. Krumbhaar, E. B., Chestnut Hill, Philadelphia.
1906. Lambert, Samuel W., 130 East 35th St., New York.
1915. Landis, H. R. M., 11 S. 21st St., Philadelphia.
1917. Lee, Roger I., Harvard Medical School, Boston.
1910. Libman, E., 180 East 64th St., New York.
1920. Litchfield, L., 5431 5th Ave., Pittsburgh.
1912. Locke, Edwin A., 311 Beacon St., Boston.
1911. Loeb, Leo, 600 S. Kingshighway, St. Louis.
1909. Longcope, Warfield T., 41 E. 70th St., New York.
1910. Lord, Frederick T., 305 Beacon St., Boston.
1905. McCrae, Thomas, 1627 Spruce St., Philadelphia.
1919. McLean, F. C., Peking Union Medical College, 61 Broadway, New York.
1919. McLester, J. S., Empire Building, Birmingham, Ala.
1905. Macallum, A.B., McGill Univ., Montreal, Canada.
1902. MacCallum, W. G., The Hopkins Hospital, Baltimore.
1920. MacLeod, J. J. R., Univ. of Toronto, Toronto, Ont.
1903. Martin, Charles F., 33 Durocher St., Montreal, Canada.
1919. Meakins, J. C., Dept. of Therapeutics, Edinburgh Univ., Edinburgh, Scotland.
1892. Meltzer, S. J., 13 West 121st St., New York.
1905. Meyer, Adolph, Johns Hopkins Medical School, Baltimore.
1917. Miller, James A., 379 Park Ave., New York.
1905. Miller, Joseph L., 122 S. Michigan Boulevard, Chicago.
1908. Moffitt, Herbert C., 240 Stockton St., San Francisco, Cal.
1915. Morris, Roger S., Cincinnati General Hospital, Cincinnati.
1917. Mosenthal, Herman O., 49 E. 53rd St., New York.

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1919. Newburgh, L. N., Univ. Hospital, Ann Arbor, Mich.
1915. Noguchi, Hideyo, Rockefeller Institute, 66th St. and Ave. A, New York.
1914. Norris, Geo. W., 1820 S. Rittenhouse Sq., Philadelphia.
1900. Novy, F. G., University of Michigan, Ann Arbor, Michigan.
1902. Opie, E. L., 600 S. Kingshighway, St. Louis, Missouri.
1918. Ordway, T., Albany Medical College, Albany, N. Y.
1919. Palmer, W. W., The Hopkins Hospital, Baltimore.
1899. Park, Wm. H., 315 West 76th St., New York.
1916. Peabody, Francis W., Peter Bent Brigham Hospital, Boston.
1918. Piersol, George Morris, 1913 Spruce St., Philadelphia, Pa.
1918. Plummer, H. S., Mayo Clinic, Rochester, Minn.
1909. Pratt, Joseph H., 317 Marlborough St., Boston.
1899. Prince, Morton, 458 Beacon St., Boston.
1894. Rachford, B. K., 1961 Madison Rd., Cincinnati.
1904. Richardson, Mark W., 67 Milk St., Boston.
1905. Riesman, David, 1715 Spruce St., Philadelphia.
1915. Robinson, G. Canby, 600 S. Kingshighway, St. Louis.
1907. Rosenau, M. J., Harvard Medical School, Boston, Mass.
1916. Rous, Peyton, 131 E. 19th St., New York.
1915. Rowntree, Leonard G., Univ. of Minn., Minneapolis.
1911. Rudolf, Robert D., 100 College St., Toronto, Canada.
1911. Russell, Frederick F., Surgeon-General's Office, U. S. Army, Washington, D. C.
1898. Sachs, B., 116 W. 59th St., New York.
1908. Sailer, Joseph, 1718 Spruce St., Philadelphia.
1919. Sellards, A. W., Harvard Med. School, Boston.
1900. Sewall, Henry, 1360 Vine St., Denver, Col.
1902. Sippy, B. W., 122 S. Michigan Avenue, Chicago, Ill.
1907. Sollmann, Torald H., 1353 E. 9th St., Cleveland, Ohio.
1916. Steiner, Walter R., 646 Asylum Ave., Hartford, Conn.
1898. Stengel, Alfred, 1728 Spruce St., Philadelphia.
1889. Stockton, Charles G., 436 Franklin St., Buffalo, N. Y.
1911. Strong, R. P., Harvard Medical School, Boston.
1917. Swift, Homer F., 65 Central Park West, New York.
1916. Taussig, Albert E., Metropolitan Bldg., St. Louis.
1897. Thayer, W. S., 406 Cathedral St., Baltimore.
1889. Thompson, W. Gilman, 61 W. 49th St., New York.
1912. Tileston, Wilder, 424 Temple St., New Haven.
1914. Wadsworth, Augustus B., 278 Yates St., Albany.
1920. Warfield, L. M., Majestic Building, Milwaukee, Wis.
1901. Warthin, Aldred S., Univ. of Michigan, Ann Arbor, Mich.
1906. Weaver, George H., 1743 W. Harrison St., Chicago.

ELECTED

1918. Webb, G. B., Colorado Springs, Col.
1912. Wells, H. G., Sprague Memorial Institute, Chicago.
1913. Whipple, Geo. H., Hooper Foundation, University of California Hospital, San Francisco, California.
1917. White, Franklin W., 322 Marlborough St., Boston.
1918. White, S. M., Donaldson Bldg., Minneapolis, Minn.
1915. White, Wm. Charles, 2851 Bedford Ave., Pittsburgh.
1901. Williams, Herbert U., University of Buffalo, Buffalo, N. Y.
1912. Wilson, Louis B., 1101 W. Zumbro St., Rochester, Minn.
1918. Wolbach, S. B., Harvard Medical School, Boston, Mass.
1917. Wood, Edward J., 201 Chestnut St., Wilmington, N. C.
1914. Wood, Francis C., 437 W. 59th St., New York.
1916. Woodyatt, Rollin T., 104 S. Michigan Ave., Chicago.

ASSOCIATE MEMBERS

ELECTED

1920. Amoss, H. L., Rockefeller Inst., 66th St. and Ave. A., New York.
1919. Cecil, R., 19 E. 65th St., New York.
1920. Dick, G., 25 East Washington St., Chicago.
1916. Edmunds, Charles W., Univ. of Michigan, Ann Arbor, Mich.
1918. Evans, J. S., University of Wisconsin, Madison, Wis.
1918. Fitz, R., Mayo Clinic, Rochester, Minn.
1919. Funk, E. H., 1318 Spruce St., Philadelphia.
1918. Giffin, H. Z., Mayo Clinic, Rochester, Minn.
1916. Hirschfelder, Arthur D., Univ. of Minnesota, Minneapolis.
1917. Lewis, P. A., Phipps Institute, Philadephia, Pa.
1916. Loevenhart, Arthur S., Univ. of Wisconsin, Madison, Wis.
1920. Macht, D. I., Johns Hopkins Medical School, Baltimore.
1919. Means, J. H., 15 Chestnut St., Boston.
1919. Minot, G. S., 188 Marlborough St., Boston.
1920. Moss, W. L., Harvard Medical School, Boston.
1919. Murphy, J. B., Rockefeller Institute, 66th St. and Ave. A, New York.
1918. Musser, John H., 338 S. 21st St., Philadelphia, Pa.
1920. Pepper, O. H. P., University Hospital, Philadelphia.
1918. Rehfuss, M. E., 16th and Spruce Sts., Philadelphia, Pa.
1916. Rosenow, Edward C., Mayo Clinic, Rochester, Minn.
1916. Shattuck, George C., 135 Marlborough St., Boston.
1920. Strouse, S., 104 South Michigan Ave., Chicago.
1920. Vanderhoof, D., Professional Building, Richmond, Va.
1919. Walker, J. C., Peter Bent Brigham Hospital, Boston.

HONORARY MEMBERS

* Original Members

ELECTED ACTIVE MEMBER	ELECTED HONORARY MEMBER	
	1920.	Allbutt, Sir Clifford, St. Radegunds, Cambridge, England.
	1916.	Gorgas, William C., Washington, D. C.
	1920.	Heger, Paul, Univ. of Brussels, Brussels, Belgium.
*1886.	1915.	Hun, Henry, 149 Washington Ave., Albany.
1902.	1916.	Kober, Geo. M., 1819 Q St., N. W., Washington.
	1920.	Marchiafava, Prof. Ettore, Rome, Italy.
*1886.	1913.	Prudden, T. Mitchell, 160 W. 59th St., New York.
	1920.	Roux, Prof. E., Pasteur Institute, Paris, France.
1892.	1920.	Smith, Theobald B., Princeton, N. J.
1889.	1915.	Vaughan, Victor C., Univ. of Michigan, Ann Arbor.
*1886.	1913.	Welch, William H., 807 St. Paul St., Baltimore.

EMERITUS MEMBERS

* Original Members

ELECTED ACTIVE MEMBER	ELECTED EMERITUS MEMBER	
1905.	1918.	Babcock, R. H., 74 East Elm St., Chicago.
1908.	1919.	Baldwin, E. R., Saranac Lake, New York.
1898.	1916.	Blackader, A. D., 236 Mountain St., Montreal.
1892.	1916.	Bolton, Meade B., Charlottesville, Va.
1898.	1917.	Brannan, John W., 48 W. 51st St., New York.
1888.	1910.	Bridge, Norman, 10 Chester Place, Los Angeles, Cal.
1889.	1916.	Cary, Charles, 340 Delaware Ave., Buffalo.
*1886.	1906.	Councilman, Wm. T., 78 Bay State Road, Boston.
1897.	1905.	Cushny, Arthur C., University of Edinburgh, Edinburgh, Scotland.
1894.	1908.	Cutler, Elbridge G., 214 Beacon St., Boston.
1888.	1916.	Dana, Charles L., 53 W. 53d St., New York.
*1886.	1905.	Edes, Robert T., 340 Summer Ave., Reading, Mass.
1901.	1919.	Edwards, A. R., 104 S. Michigan Ave., Chicago.
1888.	1919.	Ernst, H. C., 8 Greenough Ave., Jamaica Plain, Mass.
1890.	1902.	Fisk, S. A. Brimfield, Mass.
*1886.	1900.	Guitéras, John, Havana, Cuba.
*1886.	1902.	Hays, I. Minis, 268 S. 21st St., Philadelphia.
1897.	1910.	Hektoen, Ludvig, 637 S. Wood St., Chicago.
1900.	1917.	Holt, L. E., 14 W. 55th St., New York.
1890.	1902.	Hurd, H. M. Johns Hopkins Hospital, Baltimore.
1899.	1914.	James, Walter B., 17 W. 54th St., New York.
1895.	1918.	Lafleur, H. A., 215 Peel St., Montreal, Canada.
1888.	1919.	Lewis, M. J., 1316 Locust St., Philadelphia.
1891.	1920.	McPhedran, A., 151 Bloor St., W., Toronto, Can.
1898.	1916.	Mallory, F. B., Harvard Medical School, Boston.
1891.	1900.	Mason, A. Lawrence, 265 Clarendon St., Boston.
1901.	1913.	Morse, John L., 70 Bay State Road, Boston.
1891.	1918.	Northrup, W. P., 61 E. 73d St., New York.
1904.	1920.	Pearce, R. M., Rockefeller Foundation, 61 Broadway, New York.

ELECTED ACTIVE MEMBER	ELECTED EMERITUS MEMBER	
1898.	1914.	PFAFF, FRANZ, Dresdner Bank, Berlin.
*1886.	1898.	POLK, WM. M., 7 East 36th St., New York.
1903.	1918.	PREBLE, R. B., 590 Dearborn Ave., Chicago.
*1886.	1904.	ROBINSON, BEVERLEY, 42 West 37th St., New York.
1900.	1914.	SEARS, GEO. G., 19 Marlborough St., Boston, Mass.
*1886.	1912.	SHATTUCK, FREDERICK C., 135 Marlborough Street, Boston.
*1886.	1905.	SHATTUCK, GEORGE B., 183 Beacon St., Boston.
1887.	1911.	STARR, M. ALLEN, 5 West 54th St., New York.
1907.	1920.	TAYLOR, A. E., Univ. of Penna., Philadelphia.
1899.	1918.	THACHER, J. S., 20 W. 50th St., New York.
1898.	1918.	VICKERY, H. F., Ipswich, Mass.
1889.	1904.	WALCOTT, HENRY P., 11 Waterhouse St., Cambridge, Mass.
1894.	1920.	WILLIAMS, F. H., 505 Beacon St., Boston.
*1886.	1911.	WILSON, JAMES C., 1509 Walnut St., Philadelphia.
1899.	1912.	WRIGHT, J. H., Pathological Laboratory, Massachusetts General Hospital, Boston.

DECEASED MEMBERS

* Original Members

DATE OF ELECTION

1896. Adler, Isaac, New York.
*1886. Atkinson, I. E., Baltimore.
*1886. Ball, A. Brayton, New York.
1890. Barker, Fordyce, New York.
*1886. Baumgarten, G., St. Louis.
*1886. Billings, John S., New York.
*1886. Bowditch, Henry I., Boston.
*1886. Bruen, Edward T., Philadelphia.
*1886. Busey, Samuel C., Washington, D. C.
1907. Carroll, James, Washington, D. C.
*1886. Chew, Samuel C., Baltimore.
*1886. Clark, Alonzo, New York.
*1886. Clymer, Meredith, New York.
*1886. Da Costa, J. M., Philadelphia.
1889. Dabney, William C., University of Virginia.
*1886. Dalton, John C., New York.
*1886. Dana, Israel T., Portland, Maine.
1888. Danforth, I. N., Chicago.
*1886. Delafield, Francis A., New York.
*1886. Donaldson, Frank, Baltimore.
*1886. Draper, William H., New York.
1899. Ely, John Slade, New Haven, Conn.
1895. Fischel, William E., St. Louis.
*1886. Fitz, Reginald H., Boston.
*1886. Folsom, Chas. F., Boston.
*1886. Forchheimer, F., Cincinnati.
*1886. Formad, Henry F., Philadelphia.
1889. Geddings, W. H., Atken, S. C.
*1886. Graham, J. E., Toronto, Canada.
*1886. Henry, F. P., Philadelphia.
1898. Herter, C. A., New York.
*1886. Howard, R. Palmer, Montreal, Canada.
*1886. Hudson, Jr., E. Darwin, New York.

DATE OF ELECTION

*1886. Hutchinson, James H., Philadelphia.
*1886. Jacobi, A., New York.
*1886. Janeway, E. G., New York.
1908. Janeway, T. C., Baltimore.
*1886. Johnson, Hosmer A., Chicago.
1899. Johnston, W. G., Montreal, Canada.
*1886. Johnston, W. W., Washington, D. C.
1902. Kelly, A. O. J., Philadelphia.
*1886. Kinnicutt, Francis P., New York.
1901. Kinyoun, J. J., Washington.
1890. Latimer, Thomas S., Baltimore.
*1886. Leidy, Joseph, Philadelphia.
*1886. Longstreth, Morris, Cambridge, Mass.
*1886. Loomis, Alfred L., New York.
1889. Loving, Starling, Columbus, O.
*1886. Lyman, Henry M., Chicago.
*1886. McBride, Thomas A., New York.
1914. McCrae, John, Montreal, Canada.
1890. MacDonnell, R. P., Montreal, Canada.
1887. Meigs, Arthur V., Philadelphia.
*1886. Metcalfe, John T., Cold Springs, N. Y.
*1886. Miles, F. T., Baltimore.
*1886. Minot, Francis, Boston.
1898. Mitchell, John K., Philadelphia.
*1886. Mitchell, S. Weir, Philadelphia.
1887. Musser, John H., Philadelphia.
*1886. Osler, Sir William, Oxford.
1898. Packard, Frederick A., Philadelphia.
*1886. Peabody, George L., Newport, R. I.
*1886. Pepper, William, Philadelphia.
1888. Prentiss, D. W., Washington, D. C.
*1886. Putnam, James J., Boston.
1896. Reed, Walter, Washington, D. C.
1887. Reeves, James E., Chattanooga, Tenn.
*1886. Rochester, Thomas F., Buffalo, N. Y.
1889. Roosevelt, J. West, New York.
*1886. Ross, George, Montreal, Canada.
1893. Rotch, Thomas M., Boston.
*1886. Schmidt, H. D., New Orleans.
*1886. Sinkler, Wharton, Philadelphia.
*1886. Smith, A. A., New York.
1891. Smith, Andrew H., New York.
1915. Southard, E. E., Boston.

DATE OF ELECTION

1905. Steele, J. Dutton, Philadelphia.
*1886. Sternberg, Geo. M., Washington.
1896. Stewart, D. D., Philadelphia.
*1886. Stewart, James, Montreal, Canada.
*1886. Stillé, Alfred, Philadelphia.
*1886. Thacher, James K., New Haven, Conn.
1889. Thomson, W. H., New York.
*1886. Trudeau, Edward L., Saranac Lake.
*1886. Tyson, James, Philadelphia.
*1886. Ward, Samuel B., Albany.
1898. Wesbrook, F. F., Vancouver.
*1886. Whittaker, James T., Cincinnati.
*1886. Wilkins, George, Montreal.
1898. Withington, Charles F., Boston.
*1886. Wood, H. C., Philadelphia.

ASSOCIATION

OF

AMERICAN PHYSICIANS

CONSTITUTION

As Amended June 17, 1919

ARTICLE I

OBJECT AND NAME

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

ARTICLE II

MEMBERS

The number of active members shall be limited to two hundred. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

An active member whose membership has extended throughout ten years or more may, at his request, be transferred by the Council to emeritus membership.

There shall be also a class of associate members, limited in number to twenty-five, from which class active members may be elected. These associate members shall each be elected for a term of five years and shall enjoy all the privileges of emeritus members, and each of them shall pay annual dues amounting to one-half the annual dues of an active member.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

Provided, That in case of removal of an active member to a locality so distant that his attendance at the annual meetings may reasonably be regarded as impossible, the Council may be empowered, should it so desire, to transfer the name of such a member during his absence to the list of emeritus members, without regard to the length of his previous active membership.

ARTICLE III

OFFICERS

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually; five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

ARTICLE IV

DUTY OF OFFICERS

The duties of the President, Vice-President, Secretary, and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of TRANSACTIONS.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

ARTICLE V

COUNCIL

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the

Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate, and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

ARTICLE VI

MEETINGS

1. The Association shall hold an annual meeting either in the City of Washington, D. C., or at Atlantic City at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology, and miscellaneous business.

4. The President shall have complete charge of, and responsibility for, the program. He shall have power to accept or reject any paper offered. He shall have power to limit the number of papers, and to assign a time limit for each one. Papers shall be presented to the Association only in abstract, and preferably shall not be read from manuscript. They may be published in full in the TRANSACTIONS as also in any other medical publication.

5. The referee, co-referee, and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

ARTICLE VII

QUORUM

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, twenty-five shall be necessary for a quorum, and for altering the Constitution fifty members shall be necessary.

ARTICLE VIII

ELECTION OF MEMBERS

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting of the Association; and within six months of the time of nomination the

nominators shall transmit to the Council letters stating the qualifications of the nominee and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. The election of new members shall take place on the second day of the meeting. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

ARTICLE IX

ANNUAL DUES

The annual dues of the Association shall be such as the Council from time to time may fix, from the payment of which honorary and emeritus members shall be exempt.

ARTICLE X

AMENDMENTS TO THE CONSTITUTION

Amendments to the Constitution must be proposed in writing by five members at an annual meeting, and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendment; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES

OF THE

THIRTY-FIFTH ANNUAL MEETING

Held at the Hotel Traymore, Atlantic City, N. J., May 4 and 5, 1920

The following members were present at the meeting:

Allen, F. M.
Auer, John
Austin, J. H.
Barker, L. F.
Biggs, Herman M.
Blumer, George
Boggs, Thomas R.
Brill, Nathan E.
Brooks, Harlow
Brown, Philip K.
Brown, W. H.
Bunting, C. H.
Cabot, R. C.
Capps, Joseph A.
Cecil, R.
Christian, Henry A.
Cohen, Solomon Solis
Cohn, Alfred E.
Coleman, Warren
Conner, Lewis A.
Coplin, W. M. L.
Dochez, A. R.
Draper, G.
Edsall, David L.
Edmunds, G. W.
Einhorn, M.
Emerson, Haven
Finley, F. G.
Ford, W. W.
Freeman, R. G.
Friedenwald, Julius
Fulton, F. T.
Funk, E. H.
Fussell, M. Howard
Futcher, Thomas B.
Gordinier, H. C.
Griffith, J. P. C.
Hamburger, W. W.
Hamilton, W. F.
Hare, Hobart A.
Hart, T. S.
Heard, J. D.
Herrick, James B.
Hoover, C. F.
Howard, Campbell P.
Howland, John
Hunt, J. Ramsay
Hunt, Reid
Irons, Ernest E.
Jackson, Henry
Jobling, James W.
Joslin, E. P.
Kober, G. M.
Koplik, Henry
Krumbhaar, E. B.
Lambert, Samuel W.
Landis, H. R. M.
Lee, Roger I.
Lewis, P. A.
Libman, E.
Loevenhart, A. S.
Lord, Frederick T.
McCrae, Thomas
McLean, F. C.
McLester, J. S.
MacCallum, W. G.
Macallum, A. B.
Martin, Charles F.
Means, J. H.
Meltzer, S. J.
Miller, James A.
Miller, Joseph L.
Minot, G. S.
Moffitt, Herbert C.
Mosenthal, H. O.
Musser, J. H.
Newburgh, L. N.
Norris, George W.
Palmer, W. W.
Park, Wm. H.
Peabody, Francis W.
Piersol, George M.
Preble, R. B.
Rehfuss, M. E.
Riesman, David
Robinson, G. Canby
Rosenow, E. C.
Rous, Peyton
Rowntree, L. G.
Rudolf, Robert D.
Sailer, Joseph
Sellards, A. W.
Sippy, B. W.
Steiner, Walter R.
Stengel, Alfred
Stockton, Charles G.
Swift, Homer F.
Taussig, Albert E.
Thayer, W. S.
Tileston, Wilder
Wadsworth, Aug. B.
Weaver, George H.
Webb, G. B.
Welch, Wm. H.
Whipple, George H.
White, Franklin W.
White, S. M.
White, Wm. Charles
Williams, Francis H.
Wood, Francis C.

Tuesday Morning, May 4

The Association was called to order by President Biggs, who then delivered the President's address.

The Treasurer presented his report and the President appointed Drs. Tileston and Rowntree to act as an Auditing Committee.

The Secretary presented the report of the Council with the following recommendations:

1. That the dues for the coming year be $15 for Active Members who are in practice, $7.50 for Associate Members who are in practice and $5 for both Active and Associate Members in laboratory or full-time clinical work, who have no professional income apart from their salaries.

2. The list of nominations, as given elsewhere, for officers and new members.

3. That those members who had not paid the fee to the Congress for the meeting in 1919 be requested to do so and that any additional deficit be paid out of the funds of the Association.

4. That Dr. Theobald Smith had resigned the position of Councillor.

5. That Drs. A. McPhedran, R. M. Pearce, A. E. Taylor and F. H. Williams are transferred to the Emeritus list at their own request.

6. That the meeting in 1921 be held at Atlantic City on May 10 and 11.

The program was then proceeded with:

Dr. Wm. Charles White and Dr. L. O. Grondahl presented a paper on the "Refinement in Methods of Auscultation of the Lungs by Electrical Means," which was discussed by Drs. Henry A. Christian and Francis H. Williams, and the discussion closed by Dr. Grondahl.

Dr. George Draper presented a paper on "Some Observations on Chronic Arthritis," which was discussed by Drs. E. Libman, G. C. Robinson, H. A. Christian, Henry Koplik, S. Solis-Cohen and L. F. Barker, and the discussion closed by Dr. Draper.

Dr. Joseph L. Miller presented a paper on the "Effect on Blood-pressure and Blood Nitrogen of the Ingestion of Large Amounts of Fluid," which was discussed by Drs. H. Brooks, L. G. Rowntree, J. H. Austin, F. M. Allen, E. P. Joslin, A. S. Loevenhart, H. A. Christian and H. O. Mosenthal, and the discussion closed by Dr. Miller.

Dr. David Riesman presented a paper on "Acute Psychoses in Diseases of the Heart," which was discussed by Drs. George Blumer and J. B. Herrick, and the discussion closed by Dr. Riesman.

Drs. Alfred Stengel, C. C. Wolferth and L. Jonas presented a paper on "Rebreathing and Ergometric Determinations as a Method of

Estimating Cardiac Efficiency," which was discussed by Dr. L. G. Rowntree, and the discussion closed by Dr. Stengel.

Drs. S. Marx White and R. E. Morris presented a paper on the "Effects on Cats of Digitalis Lutea and Digitalis Thapsi as Noted during Intravenous Injection, with Simultaneous Electrocardiographic Tracings," which was discussed by Drs. G. C. Robinson and W. Tileston, and the discussion closed by Dr. White.

Dr. Elliott P. Joslin presented a paper on "The Total Metabolism in Diabetes," which was discussed by Drs. Boothby and F. M. Allen.

Dr. Herman O. Mosenthal presented a paper on the "Effect of Protein Food on Increased Blood-pressure," which was discussed by Drs. J. L. Miller and S. Solis-Cohen, and the discussion closed by Dr. Mosenthal.

Tuesday Afternoon, May 4

Drs. Julius Friedenwald and George H. Grove presented a paper on "The Blood-sugar Tolerance Test as an Aid in the Diagnosis of Gastro-intestinal Cancer."

Drs. Francis W. Peabody, Cyrus C. Sturgis, Edna M. Tompkins and Joseph T. Wearn presented a paper on "Epinephrin Hypersensitiveness and its Relation to Hyperthyroidism," which was discussed by Drs. M. H. Fussell and L. G. Rowntree, and the discussion closed by Dr. Peabody.

Dr. J. Ramsay Hunt presented a paper on "Acute Infectious Myoclonus Multiplex."

Drs. Wade H. Brown and Louise Pearce presented a paper on "The Production of Generalized Syphilis in the Rabbit by Local Inoculation," which was discussed by Drs. H. F. Swift and George Blumer, and the discussion closed by Dr. Brown.

Dr. E. C. Rosenow presented a paper on the "Further Studies on Influenza."

Dr. R. L. Cecil presented a paper on "Experiments with Influenza Bacillus," which was discussed by Drs. G. M. Kober, C. H. Bunting and Joseph L. Miller, and the discussion closed by Dr. Rosenow.

Drs. Elmer H. Funk and Willis F. Manges presented a paper on the "Eventration of the Diaphragm with Report of a Case," which was discussed by Drs. Ramsay Hunt, C. F. Hoover and S. J. Meltzer, and the discussion closed by Dr. Funk.

Dr. Martin E. Rehfuss presented a paper on "The Dietetic Treatment of Gastric Ulcer based on Experimental Studies," which was discussed by Drs. George H. Whipple and B. W. Sippy, and the discussion closed by Dr. Rehfuss.

Dr. George H. Whipple presented a paper on "Blood Regeneration

after Simple Anemia as Influenced by Various Dietary Factors," which was discussed by Drs. H. Brooks, C. F. Hoover, P. Rous, S. J. Meltzer and L. F. Barker, and the discussion closed by Dr. Whipple.

Drs. Peyton Rous and P. D. McMaster presented a paper on "The Hepatic Factor of Safety in Bile Elimination," which was discussed by Drs. S. J. Meltzer and G. H. Whipple.

Tuesday Evening, May 4

Dr. Samuel W. Lambert presented a paper on "Intrathoracic Teratomata," which was discussed by Drs. G. C. Robinson, J. B. Herrick and H. A. Hare, and the discussion closed by Dr. Lambert.

Dr. Francis C. Wood presented a paper on "Experiments on the Therapeutic Action of Roentgen Rays."

Drs. G. Canby Robinson and George R. Herrmann presented a paper on "Paroxysmal Tachycardia of Ventricular Origin and its Association with Coronary Thrombosis."

Dr. Walter W. Hamburger presented a paper on "The Heart in Influenza, with Electrocardiographic Studies."

Drs. M. H. Fussell and C. C. Wolferth presented a paper on "Nodal Rhythm with Reverse Block and Paroxysmal Tachycardia."

Drs. C. F. Hoover and M. A. Blankenhorn presented papers on the "Discussion of the Causal Factors for Emphysema Attending Bronchiolar Hypertonus: Non-dialyzable Bile Pigment Found in Blood."

Drs. James D. Heard and Gordon E. Hein presented a paper on the "Prognosis in Cardiovascular Diseases with Special Reference to the Application of Graphic Methods."

Dr. Max Einhorn presented a paper on "Retrograde Stretching in the Treatment of Impermeable Cardiospasm."

Drs. F. M. Allen and J. W. Sherrill presented a paper on "Chemical Studies of Edema."

Wednesday Morning, May 5

The following Officers and New Members were elected:

President—W. S. Thayer.

Vice-President—H. C. Moffitt.

Secretary—T. McCrae.

Recorder—T. R. Boggs.

Treasurer—J. A. Capps.

Council—C. F. Hoover and R. P. Strong.

Active Members—G. Draper, New York; C. A. Elliott, Chicago; J. H. Eyster, Madison; A. F. Hess, New York; A. K. Krause, Baltimore; E. B. Krumbhaar, Philadelphia; L. Litchfield, Pittsburgh; J. J. R. McLeod, Toronto; L. M. Warfield, Milwaukee.

Associate Members—H. L. Amoss, New York; G. Dick, Chicago; D. I. Macht, Baltimore; W. L. Moss, Boston, O. H. P. Pepper, Philadelphia; S. Strouse, Chicago; D. Vanderhoof, Richmond.

Honorary Members—Sir Clifford Allbutt, Cambridge, England; Professor E. Roux, Pasteur Institute, Paris; Professor Paul Heger, Brussels, Belgium; Emeritus Professor Ettore Marchiafava, Rome, Italy; Dr. Theobald Smith, Princeton, N. J.

The report of the Auditors was presented stating that the Treasurer's accounts had been audited and found correct.

Drs. F. M. Allen and J. W. Sherrill presented a paper on "Blood Analyses in Some Ophthalmic Conditions."

Drs. Paul A. Lewis and Sewell Wright presented a paper on "The Hereditary Factors in the Resistance of Tuberculosis," which was discussed by Drs. G. M. Kober, A. B. Wadsworth, G. B. Webb and S. Solis-Cohen, and the discussion closed by Dr. Lewis.

Drs. Augustus B. Wadsworth and Frank Maltaner presented a paper on "A Study of the Preparation of Antigens from Cultures of the Tubercle Bacillus for the Complement-fixation Test," which was discussed by Dr. Lewis, and the discussion closed by Dr. Wadsworth.

Dr. S. J. Meltzer presented a paper on "Irritability and Stimulation."

Drs. S. Solis-Cohen, George D. Heist and Myer Solis-Cohen presented a paper on "Observations on the Behavior of Diphtheria Bacilli in Whole Coagulable Blood in Vitro," which was discussed by Drs. E. C. Rosenow and S. Solis-Cohen, and the discussion closed by Dr. George D. Heist.

Drs. J. H. Means and A. V. Bock presented a paper on "Studies of the Acid Base Equilibrium in Disease, from the Point of View of Blood Cases," which was discussed by Dr. C. F. Hoover and the discussion closed by Dr. Means.

The following papers were read by title: "Sporotrichosis (de Beurmann) of the Lung," by Dr. William S. Thayer; "A Very Unusual Picture of the Inhibition of the Hemopoietic System," by Dr. N. E. Brill; "An Experimental Research upon the Effect of Lead on the Rabbit's Kidney," by Dr. H. U. Williams.

The following amendment to the Constitution was proposed:

That Article II relating to members be amended as follows:

There shall be a class of Corresponding Members, not to exceed twenty-five in number, to which distinguished physicians in countries other than the United States and Canada may be elected. The names of those proposed for this membership shall be put in nomination at an annual meeting by two active members and the Council shall report those nominations which are approved by it to the next annual meeting for action. An affirmative vote of three-fourths of the mem-

bers present shall be necessary for election. Corresponding Members shall be entitled to take part in the proceedings, but not to vote.

W. S. Thayer,
L. A. Conner,
T. McCrae,
W. R. Steiner,
R. C. Cabot.

On motion of Dr. Cabot, seconded by Dr. Barker, a vote of thanks was given to Dr. Biggs for the interesting program and the successful meeting which he had conducted.

Thomas McCrae, M.D.,
Secretary.

PRESIDENT'S ADDRESS

By HERMAN M. BIGGS, M.D.
NEW YORK

It has been customary for the President of the Association in opening the annual meeting to discharge briefly several obligations: The first one is the sad duty of chronicling each year the losses from death which have been sustained in the membership of the Association. During the past year four members have died. Three of these were original members of the Association, and of these three, two were honorary members—Sir William Osler and Dr. Abraham Jacobi. For more than a generation they were two of the great leaders in the scientific medicine of the world. They were men of unusual force and originality; both had striking personalities, untiring energy and extraordinary intellectual capacity. They need no eulogy in an assemblage of medical men, and least of all before this Association in the earlier years, of which they both took such an active part. Their places in the medical profession cannot be filled by others.

Dr. Horatio C. Wood, also an original member, and subsequently an emeritus member, whose death occurred during the year, was for many years active in the Association. As a leading physician, as a teacher, and as an author he is well known to you.

Dr. Elmer E. Southard, of Boston, only recently elected to active membership, died suddenly a few weeks ago, on February 9. He had expected to contribute a paper at this meeting.

The second duty which devolves on the President is a real privilege, viz., that of thanking the Council and the members of the Association for the honor of presiding over their deliberations. No one can appreciate this more deeply than I do.

Finally, it has been customary for the President to address the Association on some general topic, usually one concerning the Association or its activities or the medical profession in some of its general relations to the public or some question concerning medical education.

I desire today very briefly to bring before the Association some considerations relating to the future of medical practice, especially in the smaller cities and rural communities of the country. This has been suggested in part by the steady decrease in number of qualified physicians in these districts and in part by the lack there of the adequate hospital and laboratory facilities now required in the practice of scientific medicine and surgery. I wish to suggest a possible solution of the problem presented through the direction of future developments in medical work.

In this connection there are several fairly well-established tendencies to be considered: One of these is the evidence of a widespread demand in many parts of the United States for the adoption of legislation looking to some form of so-called "health insurance," this legislation generally being modeled, more or less on the German or British plans. The demand for this comes in part from labor leaders and in part from those chiefly interested in general social betterment. Wherever such legislation is adopted it must powerfully influence the practice of medicine.

There has also been for a long time a marked tendency in the more progressive communities for the public health authorities to include in their activities an ever-broadening field of work. This tendency seems inevitable and unavoidable whether or not it is desirable, as many physicians seem to doubt (a question which I shall not now discuss). It may be considered a practical form of governmental aid to the practice of medicine applied thus far almost wholly to the infectious diseases. The wide development of public health laboratories in recent years is a notable incident of this tendency.

As is well known, there is a gradually decreasing number of physicians in the United States, as a whole, with a marked tendency toward a greater relative depletion of the supply in the country districts and a concentration in the larger centers of population. Aside from this change in distribution there appears to be a possible

danger in the future of an actual shortage in the number of physicians in the country as a whole unless a larger number of students are attracted to the study of medicine. This is especially true if the higher standards of medical practice obtaining in our larger and best hospitals are to be applied to the care of any considerable proportion of the sick in the population outside of the hospitals. This, of course, certainly should be the aim.

The decrease in the number of medical students (amounting to more than 50 per cent.) has been brought about by the necessary elevation of the preliminary requirements for entering the practice of medicine; the longer period of study enforced, the large expenses involved and the relatively inadequate rewards offered by the profession of medicine as compared with many other pursuits. With the rapid scientific development which is going on in many departments of medicine and surgery the time required for medical study must tend to increase rather than decrease and the expenses of a medical education to be correspondingly heavier. It would naturally follow that unless the attractions of medicine are greater and the reward more substantial the best type of students—those who are particularly needed in the medical profession—will not be attracted to its study and pursuit. Furthermore, the supply of trained nurses is yearly growing more inadequate while the demand for them is rapidly expanding. Schools for training nurses are finding it difficult or impossible to obtain their quota, and the cost of nursing service is becoming so great as to place such services beyond the means of most individuals in the community. It is only in a hospital that the great proportion of the population can now have adequate nursing service.

The complete lack of domestic servants in most rural communities still further aggravates the situation when serious illness comes to one of the older members of the family even if the family is in comfortable circumstances financially, for with few physicians, no nurses and no servants, they are forced to apply for admission to a hospital to obtain any adequate care.

Then in order to obtain a complete and accurate diagnosis in cases of serious sickness, and efficient medical and surgical care, it is coming more and more to be required in a large percentage of cases

that the patient shall be admitted to a well-equipped hospital. But, unfortunately, the hospitals of the country, and especially in the rural districts, are not only totally inadequate to meet the demands but in general they are not distributed so as to be accessible to a large proportion of rural dwellers, while at the same time many of the smaller ones are inadequately staffed and equipped. Then, too, because of the greatly increased cost of hospital maintenance, a cost which must inevitably increase, existing hospitals are finding greater difficulty each year in meeting the financial demands made upon them and consequently additional hospital facilities are less liable to be provided by voluntary contributions.

There is a large, constantly increasing and unsatisfied demand at increasing salaries for well-equipped public health administrators, epidemiologists, child health experts, statisticians and well-trained laboratory workers. Very little progress is being made as yet in meeting this demand. On the contrary the total deficit in the number needed is constantly increasing. The salaries available for these positions have been insufficient to attract young medical graduates to the public health field. Happily, at present, the tendency to increases in the salaries of public health workers is marked, but these salaries are still in general quite insufficient.

It is also becoming more and more difficult each year to obtain sufficient internes and residents to staff our large hospitals and public institutions, like hospitals for the insane, etc., and there are large numbers of vacancies in the medical corps of the army and navy.

As showing how rapid is the drift of physicians from country districts, it may be noted that within the last year sixty-eight communities in New York State have applied to the State Department of Health for physicians because they had none.

In a survey recently made at my suggestion by the State Department of Health in twenty rural counties of New York State—which contained no cities and which had a population of about eight hundred thousand people—there were found to be a little over nine hundred physicians, a decrease of 15 per cent. in ten years. Of this number only about 3 per cent., twenty-six in number, had graduated within the past five years, and on the average the physi-

cians in these twenty counties had been in practice a little over twenty-five years. In one typical rural county of the most prosperous type it was found that the physicians, fifty-four in number, average in practice twenty-eight and a half years.

An investigation made by the *Journal of the American Medical Association* has shown that the average age of physicians at death is about fifty-nine years, and as all the physicians in these twenty counties on the average must be nearly fifty years of age, it is evident what the next ten years is to bring forth with reference to medical service in the districts unless conditions materially change.

In all the industrial and more highly civilized countries, there is and has been for many years a constant drift of the population from the farms to the cities. This situation has been widely recognized as one of the most dangerous tendencies of our time. It is said in New York State that there has been a decrease of 17 per cent. in the available farm labor within the last two years. In other states it has been far greater, and in Vermont it is said to be 30 per cent. The lack of proper educational facilities in rural districts in the United States has been an important factor in contributing toward this change, and if, in addition to the lack of educational facilities, there should also develop a lack of facilities for the proper care of the sick, the drift to the cities will be materially accelerated.

It seems to me evident that measures must be adopted by governmental authorities to make the practice of medicine more attractive, particularly in the smaller communities, and to make the rewards more substantial. This can only be done through state aid, as these rural communities have not the wealth to meet the situation by added necessary taxation. Any further decrease in the agricultural population is certain to render urban living conditions, already difficult, still more difficult. The wealthy cities must contribute through the state appropriations to the support of facilities for the education, the preservation of health and the care of the sick of these rural communities.

At the last session of the Legislature in New York State the writer had a bill introduced which provided state aid for the establishment of health centers in all counties and communities—the unit of population for a center being fifty thousand or major fraction thereof. These health centers would be supported in part by taxa-

tion of the district served, in part by payment of those treated and able to pay and in part by state aid. Each complete health center would consist of a hospital with pavilions as might be necessary for the care of tuberculosis, maternity cases, contagious diseases, etc.; various types of out-patient clinics, such as general medical, surgical and diagnostic clinics, clinics for children, mental and venereal diseases, etc.; laboratories properly equipped for all sorts of clinical work, including *x*-ray work; a public health nursing service covering the whole of the district; an adequate medical and nursing service in the schools and a medical library and assembly place.

The state department of health would also provide periodic consultation clinics in various departments of medicine to be held by experts to assist local practitioners in the diagnosis and treatment of difficult and obscure cases of illness. In addition to this the local authorities would be empowered to establish the district as a health district with a full-time health officer in charge. The health center would serve for all official and voluntary welfare activities of the district.

Under the provisions of this bill it would be hoped that all major surgical operations, most cases of serious acute illness and obscure forms of acute and chronic diseases or those difficult to treat, would be brought by their physicians, if they had any, to the health center for diagnosis and advice as to treatment. Those which required the facilities which it afforded would be treated there, the others, the larger percentage and all the minor ailments, would be treated at home by their physician. This seems to be rational and possibly a satisfactory solution of a problem which must be solved, and while this bill was not passed at the present session of the Legislature, because sufficient time was not available for its study and discussion, yet judging from the wide commendation and support which it received, it seems likely to receive favorable consideration at the next session of the Legislature.

The medical profession for many years has devoted much attention to the elevation of the standards of medical training. The time now seems to have arrived when attention must be devoted to making the practice of medicine more attractive and lucrative, especially in the rural districts of the country.

SOME OBSERVATIONS ON CHRONIC ARTHRITIS

By GEORGE DRAPER, M.D.
NEW YORK

No attempt will be made at this time to discuss the classification of chronic arthritis. Certain features of the disease and of some individual characteristics of its subjects will, however, be brought out for consideration. The study was developed along lines suggested by the writer's[1] experiences in the poliomyelitis epidemic in 1916 and later among the meningitis cases in the army. These experiences brought out undeniably the circumstance that there was in both diseases a remarkable uniformity in certain anatomic characteristics of the patients. The attempt to analyze this similarity in appearance by comparing each person with a "normal" was unsuccessful, because in a mixed race the normal is quite indefinite. Consequently, recourse was had to the known endocrinopathies.[2] Each patient was observed with an eye to his possession of anatomic or physiologic characteristics which, though slight, might find counterparts in one or others of the endocrine disorders.

The great frequency of the disease arthritis in women is well known. Furthermore, it is often recorded that at the time of the menstrual period patients with chronic arthritis suffer either an exacerbation of their joint symptoms or are very much better. Many cases during pregnancy lose their joint pains about the fourth month. In addition to these observations the menstrual history of women with chronic arthritis describes irregularities of one sort or another; delays, periods of amenorrhea and frequently much pain.

[1] Draper, G.: Acute Poliomyelitis, Philadelphia, 1917.
[2] Draper, G.: The Relationship of the External Appearance of the Body to Disease, New York State Med. Jour. (not yet published).

While a considerable number of cases begin with large joint involvement the small joints of the hands have been the target primarily, and often, indeed, comprised the chief articular expression of the malady in its milder forms. The changes in the joints of chronic arthritis have been divided into two main groups, productive and atrophic, but radiographs show clearly that whether joint destruction, which is the criterion of the atrophic form, be present or not there is always increase in the bony structure. This expresses itself as an increase in the bone about the joints, often thickenings in the phalangeal shanks and especially in the terminal tuftings. These important structures assume an appearance extraordinarily like that seen in cases of pulmonary osteoarthropathy. It is also analogous to the appearance of the terminal tuftings and the phalangeal shank thickenings that are present in the well-known radiographic picture of the hand of the acromegalic. It may be well to call attention here to the tendency of acromegalics to chronic bronchitis, bronchiectasis and emphysema—conditions which have been associated in turn with the terminal phalangeal changes known as pulmonary osteoarthropathy. Wright[1] reports one case of chronic bronchitis in which pulmonary signs ceased completely when the joint symptoms began, and another case in which the appearance of rales in the lungs was coincident with the onset of arthritis. One other feature which must be mentioned here in relation to the skeleton of these cases is found in the bones of the skull. Here in all five cases were found marked irregularities in the sella turcica (especially thickenings of the posterior clinoid process), all concerned with increased bone-production and an evident increase in the size of the sinuses or the density of the bone structure in the acral portions of the skull. In this connection it is of interest to record the report by Wright of a case of chronic headache which later developed chronic arthritis. The headache ceased with the onset of the joints.

The study of patients with chronic arthritis along the line of comparison with the anatomic characteristics of acromegalics brings out certain points of similarity in other parts of the body almost as

[1] Rheumatoid Arthritis, Canada Lancet, Toronto, 1911, lxv, 812.

striking as those found in the hands. In the five cases on which these preliminary remarks are based the modelling about the brow and eyes, facial bones and jaw is analogous to that of the acromegalic, to wit: prominent glabella region and supra-orbital ridges, high nose bridge and dental irregularities. All the individuals likewise showed a wide subcostal angle and in the male subject a tendency to the feminine distribution of fat and hair. The examination of the blood in these patients also shows consistently a tendency to low total leukocyte count, with the polynuclears diminished at the expense of mononuclear elements, a phenomenon commonly found also in the acromegaloid and Froelich types.

Previously more attention had been given to the thyroid gland in relation to chronic arthritis, especially by the French. Vincent[1] states that 68 per cent. of acute rheumatic fever have thyroid swelling, and believes that those who subsequently develop arthritis deformans have an associated, perhaps residual, insufficiency of the thyroid. The cases of our series have certain anatomic and physiologic markings, suggesting thyroid disturbance, such as dry skin, sweating palms, poor nutrition, nervousness and fatigability. Paul Claisse[2] has also reported the general "slowing down" of all functions in certain forms of chronic arthritis.

The sugar metabolism function of these individuals demonstrates an average or slightly diminished tolerance. In two of the cases there has been a very definite dull frontal headache following the ingestion of sugar. Several of the patients have shown a great craving periodically for candy, after eating which they developed a dull frontal headache. One patient, a male, with spondylitis, is a chronic candy fiend. An examination of the blood count following the ingestion of the glucose for the sugar-tolerance test shows no disturbance of the leukocyte count, except possibly a slight tendency to depress the total count. Several of these patients have described suffering from hives in childhood and occasionally in later life.

The cases of this series, each of which had been "through the mill" for many years in attempts to arrest or cure the disease, have

[1] Rheumatisme et opotherapie thyroïdienne, Soc. méd. de hôp. de Paris, 1908, xxv, 677.

[2] Rheumatisme thyroïdien chronique, Soc. méd. de hôp. de Paris, 1908, xxv, 675.

recently been treated in desperation by the old and homely method of the stings of honey bees. While certain definite clinical improvements have supervened in these patients, some interesting observations about the effect of bee stings have been made. It is the chief concern of this report to consider the phenomena associated with the action of the bee venom rather than to discuss its therapeutic effects.

In the first place the bee sting produces a lesion locally which is the perfect replica of an urticarial weal; later on there is generalized diffuse swelling, with redness and heat, and pain and stinging sensation which resemble the lesion of acute rheumatic fever. In two cases it was observed that fading or almost healed sting reactions on one arm, of several days' duration, developed fresh erythema and swelling within a few hours after new stings were given on the other arm. In one instance, on the seventh day following the first stings, there arose about the site of the more recent lesions typical urticarial rose-pink blotchy eruptions. In addition to this the patient had a rise of temperature, with tenderness and swelling of the lymph nodes, the whole picture typical of a mild attack of "serum sickness." Adrenalin injected at this time caused the eruption on the arm receiving the drug to subside. But the eruption on the opposite arm, like the other symptoms, was uninfluenced. Medical literature contains numerous reports of severe symptoms and even death caused by the stings of bees. There is a striking uniformity in all the accounts. In practically every case, acute and rapidly advancing swelling, syncope, weak pulse, oppression of breathing and often vomiting supervening, the edema may reach an extreme degree. No better descriptions of angioneurotic edema can be found than in these ancient records of the remarkable phenomena produced by the stings of bees and hornets. It is interesting that every case in which serious or fatal symptoms developed was stung on the face or head. At this point it is worth while calling attention to the reported chemical analysis of bee venom. Much work has been done both by J. Langer and more recently by F. Flury. The former author considers the venom an organic base precipitated by alkali, giving alkaloidal reactions and remaining undisturbed by heat up to 100° C. Flury has carried the analysis of this base

further and finds it to be a complex substance in which an indol derivative isolated as tryptophan, various fatty acids and bodies resembling saponin and lecithin have been found. None of the substances described is usually associated with the phenomena of sensitization and anaphylaxis, so that there seems for the moment to be some discrepancy between the biologic effects of bee venom

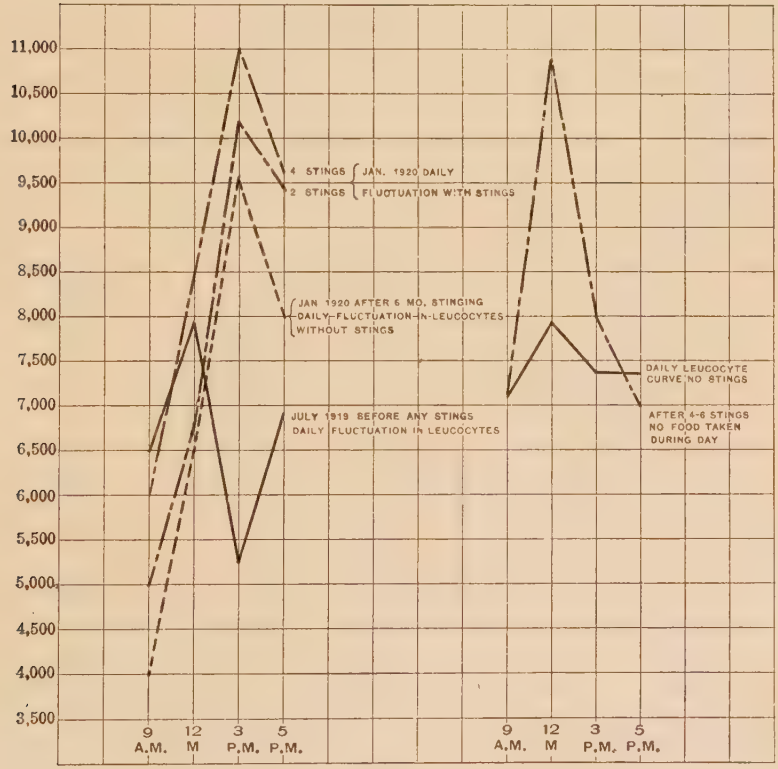

CHART I

and its chemical composition. Langer's work on the hemolytic power of bee venom and its ability to produce local necrosis exposes an analogy to certain snake venoms.

The white cell count of the blood showed interesting changes following the introduction of bee venom. Chart I shows the response of leukocytes to the venom in two cases. In the first case

the solid black line indicates the diurnal curve obtained from counts taken at 9, 12, 3, 5 o'clock, before the patient received any venom. The dotted line shows the diurnal curve six months later, after many stings and definite clinical improvement, on a day when no venom was given. The dash-dot curves show the immediate effect of the venom. In the second case the solid black line represents the diurnal curve taken at some time during the first two weeks after starting bee treatment. The dash-dot curve shows the extreme rise of the count immediately following six stings. All these counts were controlled, with special reference to the time of taking food and on the days from which the charts of the second case were taken the patient fasted all day. Very many observations were made during the year and all confirmed the fact that within fifteen minutes to half an hour after the introduction of the bee venom almost every case began to show an increase in leukocytes. The rise continued sharply for an hour or two and then fell off as rapidly. Some cases showed a delay of several hours before the rise set in. The total count is chiefly elevated, but there is also a definite increase of the polynuclears at the expense of the lymphocytes. This rise of the total count is not sustained but falls within two or three hours to the original level. Over a period of months, however, there seems to be slow, continuous and evenly sustained rise of the total count. In one case in which the bees were omitted for a period of three weeks the count fell back to its original level.

Clinically all the cases have shown a very definite improvement in their sense of well-being and in their appearance. In one case a menstrual disturbance which had frequently amounted to complete amenorrhea for as long as eight months completely cleared up. The periods were resumed and continued at normal intervals. Chronic puffiness of the eyes and ankles disappeared and the effect on the joints was also very noticeable. The subjective improvement was marked. One case had dull headaches following stings, but the joints were less affected by atmospheric changes than they had been previously. All of these patients were old stagers in the matter of knowing what real improvement was, and had been disappointed so often that they started out as complete skeptics, so that whatever value there may be in subjective improvement in the matter of

pain and discomfort is worth more in this particular malady probably than in some others.

Just what the mode of action of the bee sting is at present is comparatively obscure, but the effect upon the blood count, the skin reactions and the reports of generalized edema and the temperature rise suggest acute protein shock analogous to the effects obtained by injections of many foreign proteins. Artificial bee stings composed of various dilutions of formic acid produce the same, though

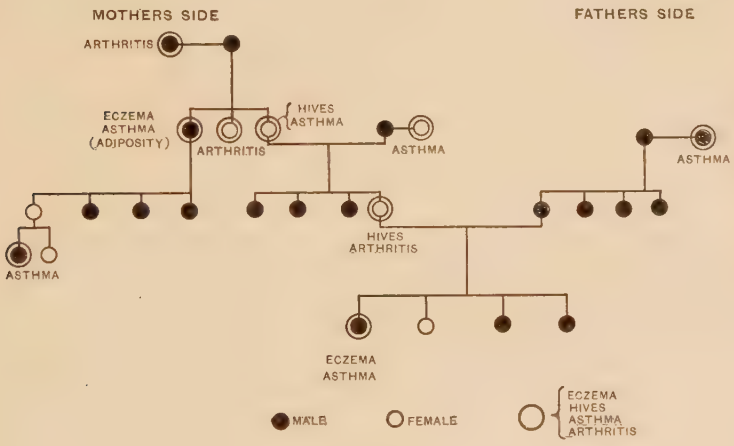

CHART II

much milder, local effect than the true bee sting does and no constitutional changes. The indication that sensitization processes are concerned and the consideration of the analogy of the bony changes to those associated with pulmonary conditions led to inquiry for the presence of asthma, urticaria and eczema in the patients themselves or in members of their families. Chart II illustrates, in striking fashion, the intense predisposition to the disturbances under discussion, which runs through the family tree.

Consideration of all these points leads to the conclusion that chronic arthritis represents a very profound constitutional disturbance in which forces analogous to those concerned in acromegaly and thyroid insufficiency are concerned. The family and personal history which arthritic patients give of hives, angioneurotic edema

(bee sting effects) and asthma, and, in addition, the well-known feature of joint involvement seen in serum disease, all seem to indicate that there is a relationship between this whole group of phenomena and chronic arthritis.

DISCUSSION

Dr. Emanuel Libman, of New York, said he believed there were very important points in Dr. Draper's paper. He thought, personally, that infection attacked the joints because of a previous condition of the patient, the ductless glands having been the cause of disturbed metabolism. Dr. Draper had said that he found arthritis was associated with a sort of subthyroid condition. This had been previously discussed under diatheses, but one had also to account for those metabolic disturbances. Certain physicians thought of certain diseases in patients of a certain type. Dr. Delafield used to say, in regard to dysentery, that he could look at a man in New York and tell what was the matter with him, although he might not be able to do that in Chicago or in Manila. This question no doubt had a bearing on drug idiosyncrasies. One could look at an individual and say what idiosyncrasy he would present to a certain drug.

Dr. G. C. Robinson, of St. Louis, said he was very much interested in hearing Dr. Draper speak of a patient's reaction to bee stings. During a trip in the mountains of Pennsylvania one of the party had been stung by a hornet and five minutes after developed intense edema of the face, difficulty of vision, urticaria and general weakness. After half an hour vision improved. There was a intense urticaria all over the body and a rapid and weak pulse. This may have been some form of anaphylactic reaction.

Dr. Henry A. Christian, of Boston, said that Dr. Walter had made charts showing the heredity in cases of asthma, and from his studies had come to the conclusion that the factor that was hereditary was the protein sensitization. There was no inheritance of sensitization to any particular form of protein; many of the individuals had no symptoms and no disease, except sensitiveness to one or another protein. Many others had asthma. Arthritis was common. No particular disease might be inherited, but the general principles of inheritance of sensitiveness seemed to correspond to the Mendelian law.

Dr. H. Koplik, of New York, said that a large number of children suffered from asthma and many gave reactions to sugar in the form of

eczema. An outbreak of eczema would relieve the asthma. Often one could trace in the parents of these children a sensitization. They were affected with "acidity" and showed local spots of eczema Some of the children complained of joint pains; these did not have asthma, so that it seemed as if this reaction was selective and attacked certain children in certain organs.

Dr. S. Solis-Cohen, of Philadelphia, said that this was all part of a much larger question. There was a peculiar inherited familial liability to certain disturbances of the autonomic nervous system, and the endocrine glands, which manifested itself in different groups, in different families, in different members of the same family and in one individual at different periods of time, under varying conditions. The difference in aspect depended upon two additional factors: one was the difference in the special exciting cause and the other was the conditions determined in the individual himself. These cases should be analyzed from three standpoints: (1) Hereditary liability; (2) particular exciting cause; (3) particular local determinant. Osler in his studies in 1887 pointed out the whole relationship of these disturbances in sensitive persons. He discussed horse asthma, hay fever, pseudo-appendicitis, angiospasms, etc., in a group of persons who have a tendency to metabolic disturbances and present insufficient carbohydrate and fat metabolism. Persons who showed glycosuria and diabetes seemed to have a distinct resistance to tuberculosis and to carcinoma. On the other hand individuals suffering from carcinoma or tuberculosis escaped these disturbances. Dr. Cohen said he could not pretend to give the explanation, but the facts were very noticeable. This discussion only took in a corner of a very large field.

Dr. Llewellys F. Barker, of Baltimore, said he thought Dr. Draper in his paper had made a very laudable attempt to correlate disposition to infection and the effects of infection. In discussing constitutional make-up one should ask how far did constitutional peculiarities make the individual liable to infection and how far did endocrine disturbance modify the make-up after infection had taken place. In regard to the arthritic diatheses: There was evidently a predisposition to arthritic infection. That the endocrine glands had much to do with external habit was established, but one should study the endocrine make-up preceding the infection. Arthritis often led to endocrine disturbance. The thyroid was upset by infection and responded by hyperplasia. Infection in the lungs might be through hypophyseal disturbance. It was difficult to disentangle how much disturbance preceded infection and how much was secondary to it.

Dr. George Draper, of New York, (in closing), said that this was a very complex problem. Dr. Robinson had spoken of edema of the face following

a hornet's sting. In the literature, sudden deaths had been recorded from bee stings about the head, although such persons had been previously stung about other parts of the body without bad result. This discussion had automatically turned into one on asthma. Dr. Koplik had mentioned the alternation between eczema and asthma. There was evidently a pituitary influence in the asthmatic and the skin disturbance might possibly be adrenal in origin. Dr. Barker had summarized the whole situation as far as infection was concerned.

INTRATHORACIC TERATOMATA

By SAMUEL W. LAMBERT, M.D.
AND
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A SERIES of cases has recently come under the observation of members of the medical staff of St. Luke's Hospital which has led to some studies in clinical diagnosis and in pathology of unusual interest. Three of these cases occurred in the medical service and two were discovered in the department of roentgenology. All five have been grouped under the general heading of congenital neoplasms or teratomata of the thorax. In addition a case occurring in the service of Professor Longcope at the Presbyterian Hospital has, through his courtesy, been added.

The histories of these cases are as follows:

CASE 1.—P. L. Male, hod-carrier. Aged forty years. Married. First seen April 14, 1916.

Family History. Six of his children died of infectious diseases and two are now living and well. His wife has had two miscarriages.

Past History. Was stabbed in the chest twenty-two years ago, spat blood at the time of injury and was sick one week. Admits gonococcus and doubtful luetic infection. Very moderate user of alcohol. Has been thirteen years in the United States.

Present History. Has had constant pain in the left side of the dorsal region, passing forward to the epigastrium, which is worse one to two hours after eating and in bad weather; there is no vomiting; appetite is poor and bowels are regular; pain interferes with work. Sleeps well; pain is bad on waking and is not increased by walking, but bad when sitting or lying on the side. There is no cough, no sweats, no dyspnea, no bladder symptoms, no palpitation, no hemoptysis and no dysphagia.

Patient has been deaf in the right ear for two years. There is no loss of weight.

Physical Examination. Patient is a well-nourished man, with good color and weight of 150 pounds. *Lungs:* No changes in breath or voice sounds and no rales are heard; there is dulness to the left of the sternum from the second rib downward continuous with the cardiac dulness and extending to the left for three inches from the midline of the sternum. *Heart* is not enlarged; no murmurs are heard in the heart or over the area of dulness on the anterior chest wall. *Liver* edge is felt. *Spleen* is not felt. *Knee-reflexes* are present and not exaggerated. *Pupils* react; the right is slightly larger than the left. *Spine* shows no tenderness nor irregularities and there is no kyphosis. There is a scar on the back of the right chest, in the scapular line, over the ninth rib. *Blood:* Hemoglobin is 100 per cent.; red blood cells, 5,450,000; white blood cells, 9400. The differential count shows polynuclears, 56; small lymphocytes, 34; large lymphocytes, 8; eosinophiles, 2. Wassermann reaction is negative (April 22, 1916). This was repeated several times and after antiluetic treatment was negative twice (May 31 and August 18, 1917) and doubtful positive once (October 31, 1918). *Urine:* Specific gravity 1.023; reaction acid; albumin and sugar negative. *Blood-pressure* is 126 systolic, 76 diastolic and equal in both arms.

The radiographic examination shows a rounded shadow extending above and to the left of the heart, 13.5 cm. from the midline of the body, which does not pulsate and which has a broad (6 cm.) extension downward in the midline behind the heart and reaching to the dome of the diaphragm. A side view shows the anteroposterior contours of the tumor to be also globular and situated behind the arch of the aorta and the heart. The posterior aspect of the mass fits into a sort of bed on the anterior surfaces of four of the vertebræ, which are deformed in a symmetrical curve. It would seem that this development occurred during growth and that the spinal bones had been prevented from attaining their normal shape by the pressure of this neoplasm. This deformity presents a smooth, even surface, and in no sense can it be considered as an erosion or an inflammatory process.

The patient has remained in good health except for recurring attacks of pain of a mild character. He has returned to work and carried a hod still in April, 1920. On April 11, 1920, the physical signs were unchanged from those of four years ago and a radiographic study of his thorax shows no changes from those originally found and described above. The original diagnosis of teratoma in the posterior mediastinum seemed justified by the presence of a large, smooth, globular tumor behind the heart, which has apparently caused by its mere presence a developmental failure to grow normally in the bodies of the fourth, fifth, sixth and seventh dorsal

vertebræ and has compelled these bones to form a concave surface on their ventral borders closely applied to the posterior surface of the tumor.

This diagnosis is substantiated by an entire lack of growth in the tumor during the four years of observation and by the possibility, by *x*-ray examination, especially from the side viewpoint, of showing no pulsation in the mass and of separating the tumor from the arch of the aorta lying in front of it. The absences of pulsation, of thrill, of murmurs, of tracheal tug and of radial pulse variation are also confirmatory, although the radiograph taken in front places the tumor in the possible location of an aortic aneurysm.

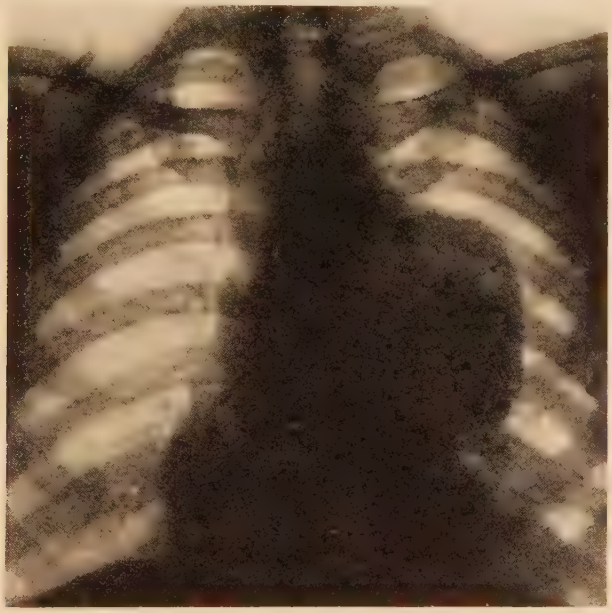

FIG. 1.—Anteroposterior radiograph of Case 1. Solid teratoma. December, 1916.

The plates show the radiographic shadows in Fig. 1 as taken from the back, in Fig. 2 as taken from the side. The spinal deformity referred to is seen in Fig. 2. Fig. 3 was also taken from the back three and a quarter years after the radiograph shown in Fig. 1. The measurements of the tumor are the same on each plate.

CASE 2.—G. S. Male. Aged forty-seven years. Married. Born in the United States. Admitted December 5, 1917.

Family History. Mother died of tumor of the stomach. Eleven brothers and sisters alive and well; father alive and well. No history of tuberculosis in the family.

Past History. No alcoholic or tobacco excess. Five children alive and well. Wife has had no miscarriages. Wassermann in wife and children negative. Had chancre and gonorrhea twenty-five years ago and received no treatment until ten years ago. Since then he has been very regular in taking treatment by mercury and iodide. Nine salvarsan injections have been given in the past three years. The blood Wassermann was said to be ++++ two weeks ago.

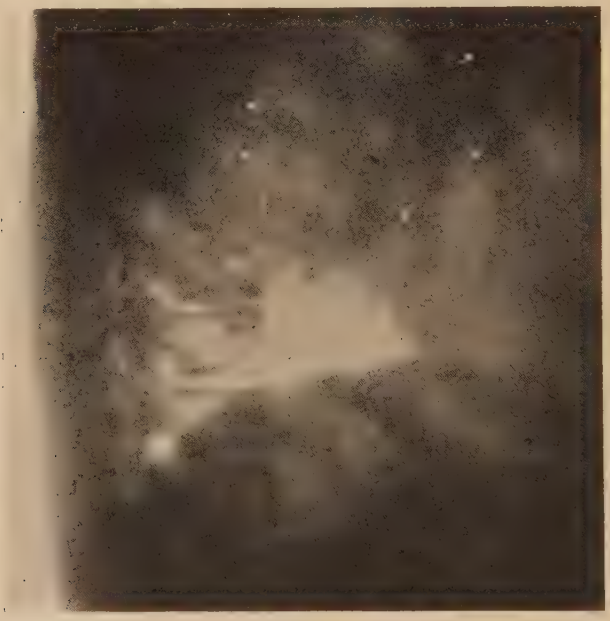

FIG. 2.—Lateral radiograph of Case 1. Solid teratoma. April, 1920.

Present Illness. Patient for two and a half months has had pain in the epigastrium after meals; the attacks last one hour, radiate to the back and are relieved by eating. Two weeks ago a sudden faintness was followed by vomiting of two cupfuls of clotted blood and later by tarry stools. He has occasional numbness and shooting pains in the legs, but no headaches.

Physical Examination. Lungs negative. *Heart:* Dulness not enlarged; systolic murmur is present over one-third of the right intercostal space at the sternal edges. The second aortic sound is louder than the second pulmonic. Above the heart there is a central area of dulness two inches to the right and three inches to the left of the midline extending up to the first costal interspace. No murmurs, thrill or pulsation over the dulness;

no tracheal tugs are observed and the radial pulses are equal. *Blood:* Hemoglobin, 70 per cent.; red blood cells, 3,900,000; white blood cells, 12,500, with a differential count of polynuclears 64 and lymphocytes 36. The blood-pressure is 140 systolic and 80 diastolic. *Urine:* Specific gravity, 1.025; albumin, very faint trace; sugar, negative; few casts; no acetone bodies. Spinal fluid contains five cells and has a flat, colloidal gold curve. Spinal fluid Wassermann is negative; blood Wassermann is also negative. Eye-grounds are negative. Blood-pressure is equal in both arms.

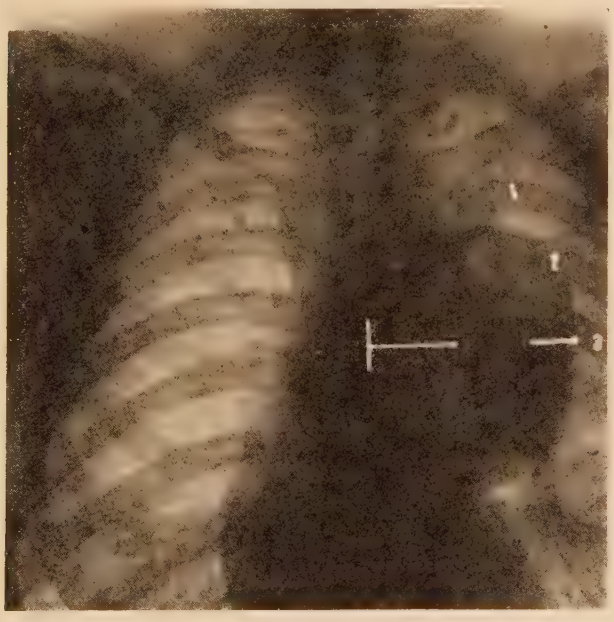

FIG. 3.—Anteroposterior radiograph of Case 1. Solid teratoma. April, 1920.

December 15 the patient fainted while at stool on a bed-pan. Thirteen, fifteen and eighteen hours later he vomited black blood clots (32 ounces in all). After the hemorrhage the blood hemoglobin was 35 per cent.; red blood cells, 2,000,000; white blood cells, 12,500; with a differential count of polynuclears 86 and lymphocytes 14. The patient gradually recovered from the loss of blood. The radiographic examination showed a shadow between the second and fifth ribs; the shadow has smooth borders and is conical in shape; to the left it extends 7 cm. from the median line between the first and third ribs. To the right it extends 9 cm. from the midline. It is ovoid and smoothly rounded; under the fluoroscope there is only doubtful evidence of pulsation.

December 26 the stool was free from blood for the first time.

January 16 the blood had a hemoglobin of 65 per cent.; red blood cells, 3,500,000. In spite of several negative Wassermann tests of the blood the patient was treated by mercury and received one treatment, both intravenous and intraspinal, with arsenobenzol February 8, 1918. This was repeated March 8, April 12, July 15, September 9, November 6, December 29, 1918, February 3, 1919, March 19, April 29, June 1 and September 15, 1919.

FIG. 4.—Anteroposterior radiograph of Case 2. Solid teratoma. December, 1917.

July 15, 1918, the blood examination showed a hemoglobin of 85 per cent.; red blood cells, 4,300,000; white blood cells, 10,000, with a differential count of polynuclears, 82; lymphocytes, 16; eosinophiles, 2. The Wassermann test was negative.

September 15, 1919, the patient was in the hospital for the last time. He had improved in general condition but asthmatic attacks had developed and a pressure cough had increased in severity during the past year; dyspnea had increased, especially while lying on the right side. There has been no hemoptysis. He has lost ten pounds in weight.

On physical examination the blood is not anemic; the hemoglobin, 98 per

cent.; red blood cells, 4,800,000; white blood cells, 9700, with a differential count of polynuclears 74 and lymphocytes 26.

The original diagnosis of aneurysm did not seem to be confirmed by the subsequent study of the chest by *x*-ray examinations. No change in size was demonstrable in several examinations between December, 1917, and September, 1919, and no pulsation was seen at any time in the fluoroscope. No auscultation signs of aneurysm were discovered in frequent examinations. The patient left the hospital September, 1919. His cough became somewhat troublesome, but his health was not seriously impaired up to the time of death. He died suddenly, two months later, without evidence of internal hemorrhage. An autopsy was not permitted.

FIG. 5.—Anteroposterior radiograph of Case 2. Solid teratoma. August, 1919.

The diagnosis of aneurysm seems possible for the left central portion of the tumor mass in this case, but the peculiar shape, the lack of growth, the absence of pulsation and of murmurs seem to justify the diagnosis of a teratomatous tumor for the right-sided mass if not for the whole mass itself.

Fig. 4 shows the condition as observed December 7, 1917, and Fig. 5 gives the chest shadows as found August 2, 1919. A comparison of these two plates shows the absence of changes during a period of twenty months.

Case 3.—E. J. B. Male. Aged thirty-four years. Born in the United States. Married. Admitted January 21, 1919.

Family History. Father died of "cancer of the hip;" mother died of unknown causes; one brother and one sister died of nephritis.

Past History. Five years ago the patient had a cold in the back and was sick one week. There have been no other illnesses except the diseases of childhood. He has had slight gastric indigestion, with occasional vomiting of food, but no blood in the vomitus; no severe pain; no cough; no hemoptysis; no edema. He is constipated. He had a chancre eighteen

Fig. 6.—Anteroposterior radiograph of Case 3. Solid teratoma. January, 1919.

years ago but no Neisser infection. His habits include ten cigars a day and very moderate use of alcohol. He has one child alive and well; his wife has had no miscarriages. He lost fifteen pounds in the past five months, with occasional night-sweats. He has been short of breath for one week. For one month following a fall from a ladder he has had pain in the front of the chest and later around the left shoulder and upper back part of the chest. He has had no fever or chills. His pain is not worse on breathing.

Physical Examination. There is flatness over the left upper front of the chest; breath sounds are absent and whisper is bronchial. Dulness with

diminished and distant bronchial breathing and whisper are found in the scapular region. There is flatness, absence of fremitus and diminished breath sounds at the left base behind. The right chest is resonant with sibilant breathing in front and with bronchovesicular breathing and whisper and subcrepitant rales at the angle of the right scapula. *Heart* is displaced to the right; all sounds are muffled; no shocks and no thrills are found. Right border of the heart is 5 cm. to the right in the third space. Pulses in both radials are about 100 and are equal; no tension; no tracheal tug is discovered. The *liver* is enlarged 3 cm. below the ribs. The right *kidney*

FIG. 7.—A drawing showing relation of teratoma to thoracic contents from Case 3.

is felt, *spleen* is not felt, but there is no ascites and no edema. The *knee-reflexes* are normal. Temperature and respiration are normal. *Urine* shows no albumin and no sugar. *Blood* shows a hemoglobin of 85 per cent.; red blood cells, 4,600,000; white blood cells, 9000, with a differential count of polynuclears 80 and lymphocytes 20. The blood-pressure is 135 systolic and 95 diastolic. The Wassermann in the blood is negative. The colloidal gold curve is also negative. A test puncture of the left chest showed a bloody fluid.

The radiographic examination showed a rounded shadow in the upper part of the left chest covering the whole breadth of the chest and presenting a border downward, which seems to represent a spheroidal mass lying above the heart and to the left, which compresses the upper lobe of the left lung. There is a shadow in the lower left chest, which was interpreted as free fluid. Fig. 6 shows the radiographic shadows as they existed January 24, 1919.

The pain continued, was referred to the chest and required sedatives; the patient grew weaker rapidly and died, after ten days' observation, of cardiac failure, following two sudden attacks of dyspnea and cyanosis at intervals of one hour.

Autopsy. The left pleural cavity contains 1 liter of clear straw-colored fluid. The upper part of the mediastinum is occupied by a mass as large as a cocoanut situated above the heart and extending into the dome of the left pleural cavity. The left lung is compressed and adherent to this mass, but is not involved in it. The mass is rather nodular on the surface and on incision is found to be made up of a grayish-white, rather juicy substance with hemorrhagic areas. The heart is negative. The right lung is edematous and shows numerous elevated nodules, a few millimeters to 1 cm. in diameter. The left lung is completely atelectatic and its surface is studded with small, elevated nodules. The parietal pleura on the left side shows a number of elevated, reddish nodules a few millimeters in diameter (Fig. 7). The liver shows a few elevated reddish nodules from a few millimeters to 1.5 cm. in diameter, which on incision are made up of hemorrhagic tissue. The liver parenchyma appears somewhat granular and fibrous. The spleen, kidney and prostate show nothing noteworthy.

Anatomic Diagnosis. Teratoma of mediastinum. Metastases of pleura, lung and liver. Pulmonary edema and congestion.

The microscopic examination of this tumor and its metastases, studied by one of us (Dr. L. C. Knox), is given in detail below under the subheading of histopathology. It is sufficient to note here that the tumor contained elements of skin, of intestine and of the central nervous system as well as muscle, cartilage, bone and teeth and that the malignant character of the growth was that of a typical chorio-epithelioma, so that this tumor must be classed as a teratoma, which is formed of all three embryonic layers and of the fetal envelopes as well.

The following cases have been observed at the New York University by Dr. L. T. LeWald, who has also done the radiographic work on the cases from St. Luke's Hospital.

Case 4.—J. W. White. Male. Aged nineteen years. Single. Laborer.

The patient came to the clinic of the New York University and Bellevue Hospital Medical College January 25, 1916, complaining of headaches, and

stated that he had had headaches off and on for a period of two years, which had gradually increased in severity. In the course of a routine physical examination made by Dr. E. J. Riley it was discovered there was dulness over the left side of the chest, with obscure physical signs. The Wassermann examination was negative. A radiographic examination of the case showed a shadow to the left of the median line and above the left auricular shadow. It extended about 9 cm. to the left of the median line and about 10 cm. in vertical diameter. The edges were rounded and the lower border was superimposed upon that of the left ventricle. The

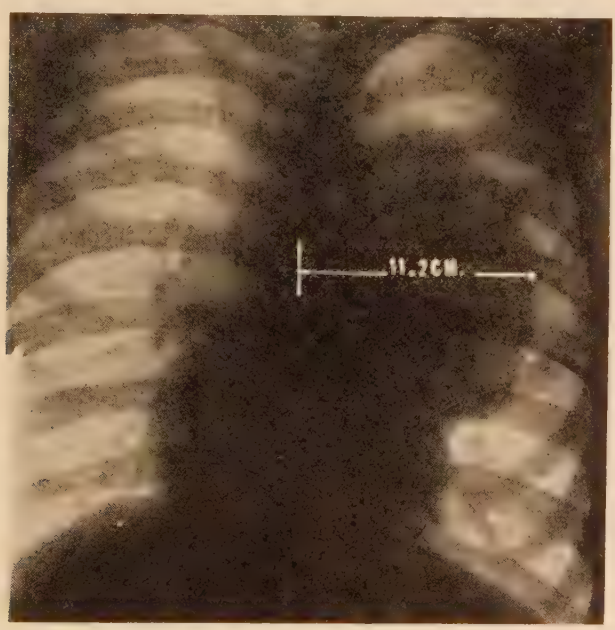

FIG. 8.—Anteroposterior radiograph of Case 4. Dermoid cyst. January, 1916.

shadow was as dense as the heart shadow. On fluoroscopic examination the portion of the mass near the heart seemed to show some movement, but it was probably transmitted from the heart. No definite expansile pulsation was made out. November 16, 1916, a second examination was made which showed a slight increase in the dimensions of the chest tumor. A third examination showed, March 5, 1919, a marked increase in the size of the chest tumor. It had reached nearer to the surface of the chest, having increased about 3.3 cm. in all directions. The heart was pushed to the right. It would seem that this case represented the commoner

form of congenital tumor and that it was a true dermoid of the anterior mediastinum. Fig. 8 represents the radiograph of January, 1916, and Fig. 9 that of March, 1919. The gradual growth of the tumor is clearly demonstrated. The diameter of the tumor shadow has increased in thirty-eight months from 11.2 cm. to 14.5 cm.

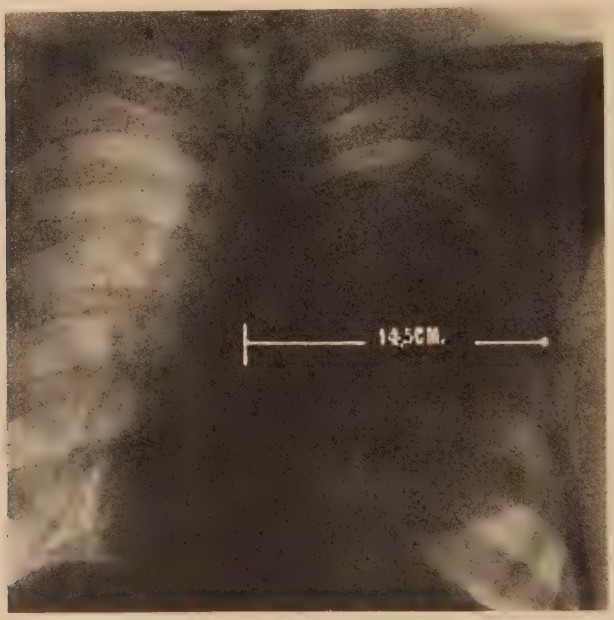

FIG. 9.—Anteroposterior radiograph of Case 4. Dermoid cyst. March, 1919.

CASE 5.—J. K. Married. Male. Aged thirty-seven years. Plasterer. Born in Russia.

This patient came to the clinic of the New York University and Bellevue Hospital Medical College July 19, 1917. He stated he had been ill for five months with pain in his chest. On further questioning a statement was made that he had had pains in his chest for twenty years. Physical examination made by Dr. Margaretten disclosed dulness below the left clavicle. The Wassermann examination of his blood was negative. An *x*-ray examination made by Dr. Le Wald disclosed a mass in the left side of the chest measuring about 8 x 12 cm. in diameter, extending from the heart shadow toward the lateral wall of the chest and about equal in density with the heart shadow. The edges were smooth and no expansile pulsation was observed. The case was observed for a period of about

one year and no change in the size of the intrathoracic mass was seen. This patient came under observation in the Presbyterian Hospital December 17, 1918, and the subsequent history as given in the hospital reveals the following:

Patient was admitted with a temperature of 102.8°, pulse 106 and respirations 46.

The chief complaint was a pain in the chest of thirty-six hours' duration.

The *present illness* was sudden in onset, with sharp, severe, pleuritic pain, dyspnea, chill, fever, cough, malaise and prostration and bloody expectoration. The cough and deep inspiration made the pain worse. He had pneumonia two years ago, with no cough since that attack.

Physical Examination. The patient is a well-nourished, middle-aged man, apparently very sick. *Eyes:* Mucous membrane of conjunctivæ slightly reddened. Pupils react to light and accommodation. *Mouth:* Tongue is heavily coated, brown and dry. Teeth are in bad condition, with some pyorrhea. Tonsils are not enlarged. *Heart:* Regular. Moderate force. Apex-beat in fifth left interspace 9 cm. from midline; no enlargement; sounds are scarcely heard; no murmurs or friction rubs are found. Pulse is small, weak, regular and easily compressible. *Lungs:* Breathing is somewhat labored. Expansion is poor. Rasping frequent cough, which is productive. Over the right lung anteriorly there is a very loud compensatory breathing; a resonant note on percussion; and fremitus is present; no rales are heard anterior to the anterior axillary line, where there are many small fine moist rales on inspiration. Over the right lobe posteriorly there is slightly diminished breathing and a fairly resonant note on percussion, also a tactile fremitus and quantities of subcrepitant rales. Over the left lung anteriorly there are also quantities of subcrepitant rales, no diminution in resonance of percussion note and the fremitus is normal. Over the left lung posteriorly there is diminished resonance on percussion, markedly diminished breath sounds and quantities of moist rales, small and medium in size. *Abdomen:* Symmetrical and quite distended. Liver and spleen are not palpable. No points of tenderness or masses are found. *Reflexes:* Knee-jerks are very active. *Diagnosis* on admission was bronchopneumonia. *Analyses:* Sputum for pneumococcus grouping (December 18, 1918) showed a hemolytic green streptococcus which was recovered in pure culture from a mouse. Sputum for tuberculosis is negative in several examinations. Blood Wassermann is negative. Blood count: Red blood cells, 5,352,000; hemoglobin, not done; white blood cells, 20,600. Differential count on 100 cells showed polynuclears, 84; large lymphocytes, 5; small lymphocytes, 11.

December 23, 1918, the signs were clearing rapidly. Only an occasional rale, mostly in the upper left lobe and the right lower lobes. A profuse greenish, foul sputum. The general condition was good.

December 27, at 4 P.M., there was a distinct rise in temperature and pulse. Temperature was 101.8°, respirations 20, pulse 80. At 4.45 P.M. the patient coughed up six to eight ounces of greenish, thick, very foul-smelling fluid. He coughed greatly for a while, raising small amounts of material of the same quality. The patient could not be examined carefully, but in the left lower lobe there were many coarse wet rales. Coughing became quieted with patient lying on his left side.

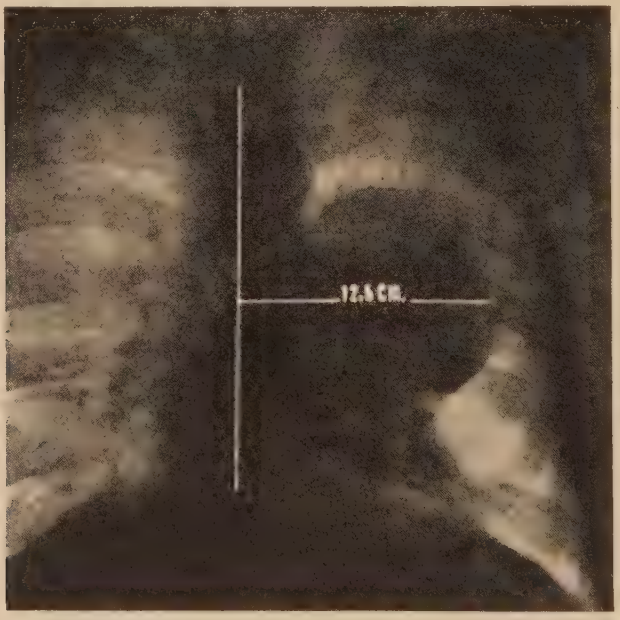

FIG. 10.—Anteroposterior radiograph of Case 5. Dermoid cyst. July, 1917.

December 28, over the left anterior chest in the second and third spaces, there are signs which suggest cavity. There is cracked-pot resonance, diminished breath sounds and a great many coarse moist rales, especially after coughing; there is postural change in pitch, suggesting a cavity containing fluid. At the right base there are still profuse signs.

The temperature disappeared slowly and the patient made a good convalescence. On January 7, 1919, the lungs were practically clear of signs. A letter from the patient under date of May 15, 1920, states that he feels well, is able to work and considers himself cured. He states he never coughed up material resembling hair.

Fig. 10 shows a distinct tumor mass in the root of the left lung as exist-

ing on July 19, 1917, and a second radiograph taken fourteen months later, September 13, 1918, shows identical findings. Three months later, after an attack of fever in December, 1918, during an indefinite bronchopneumonia, the patient coughed up a large amount of pus, and an *x*-ray picture (Fig. 11) taken the next day shows a distinct abscess cavity at the location in the chest of the tumor mass discovered.

The diagnosis of dermoid cyst, which became infected and ruptured into a bronchus seems justified by the comparative study of the radiographic plates.

FIG. 11.—Anteroposterior radiograph of Case 5. Abscess of mediastinum, December, 1918.

CASE 6.—J. McN. Female. Married. Aged fifty-four years. Born in Ireland. Admitted to the Presbyterian Hospital April 2, 1919, complaining of a dragging feeling in the left upper quadrant during the previous fourteen months. She had had a cough for the past three weeks.

Family History. Mother and father died in old age. Four sisters are living. No serious illnesses. Husband is living.

Personal History. Average weight 130 pounds, now 130½ pounds. Takes six cups of tea and one cup of coffee a day, but no alcohol. She sleeps poorly; appetite is good; bowels are regular; she takes an occasional catharsis. She had done no work in the past eleven months.

Past History. She had had measles and pleurisy. No accidents. Thirty years ago she had her left thumb amputated. She has had three children, one of whom died of pneumonia. No miscarriages. Menopause occurred twelve years ago, when the patient was forty-two years old.

Physical Examination. Patient is a thin, poorly developed woman, aged about fifty years. She does not appear to be in good health. *Eyes:* Pupils are equal and react normally. *Chest:* Heart is not enlarged; sounds are regular; no murmurs are heard. *Lungs:* Numerous coarse moist

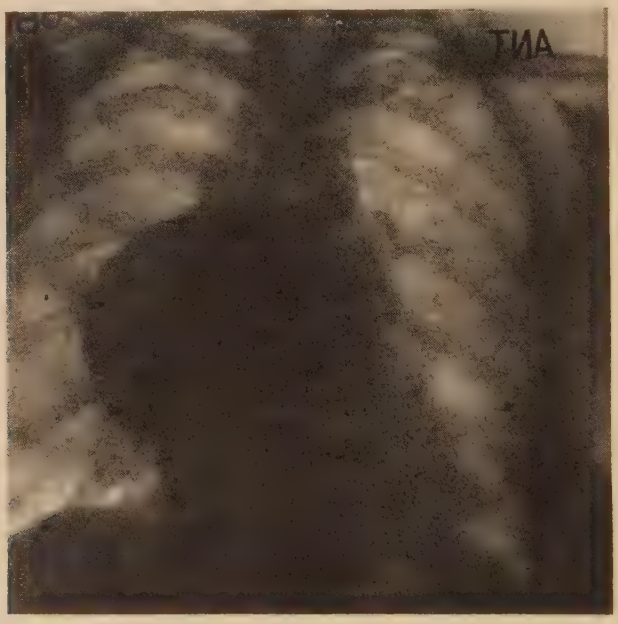

FIG. 12.—Anteroposterior radiograph of Case 6. Calcified dermoid cyst. April, 1919.

rales are heard over both upper lobes anteriorly; over the right lung in front the percussion note is dull from the fourth space to the liver dulness. This area extends almost to the anterior axillary line. Over the dull area the fremitus and the voice and breath sounds are markedly diminished. *Abdomen:* Liver is palpable, otherwise negative. *Extremities:* Knee-jerks are active; there is no edema. *Sputum:* Tuberculosis is not found. *X-ray report:* A dense circular shadow is superimposed upon the central portion of the thorax which seems to indicate that it lies in the anterior chest wall. There is a distinct curvature of the spine to the right.

The tumor is probably an osteochondroma. *Blood count:* White blood cells are 12,200, polynuclears 66, small lymphocytes 18, large lymphocytes 14, transitionals 1, eosinophiles 1. The Wassermann reaction is negative.

Fig. 12 shows a tumor in the anterior mediastinum which seems to be either a dermoid with marked calcification of its wall, or a solid teratoma.

Diagnosis. The diagnosis of these cases does not present the same difficulties that existed before the systematic use of the *x*-ray became a routine procedure. The history of these tumors is fairly characteristic and can be followed by serial *x*-ray examination. They all, both dermoid cysts and teratomata, are embryonic in their origin and exist in the body of their host at birth. During childhood they are subject to the same influences of growth as the host and grow slowly until puberty, at which time they frequently increase in size rapidly, so that in many cases they present clinical symptoms either before or soon after puberty is passed. The nutrition of these tumors is dependent on the circulation of the host, and they give no symptoms, in most cases, except those of pressure on neighboring organs. As soon as the normal growth development of the host or autosite is completed that of the teratoma or parasite usually becomes quiescent and the tumor remains as a parasitic structure which shows no tendency to grow or develop during the remainder of the life of the host, so that the symptoms of pressure are at no time a prominent feature and in many cases these tumors are discovered only by a chance examination of the patient.

Two elements may come in to disturb this usual course; they may continue to increase in size after puberty. This happens whenever the secretion from the deformed skin surfaces lining the cystic portions of the tumor becomes increased in amount. Pressure symptoms on other structures become prominent or even developed for the first time as a result of this activity. They may, on the other hand, remain quiescent for many years and then some embryonic element may take on a malignant character and a form of neoplastic growth be added to the structures of the tumor mass. Carcinoma and sarcoma with metastases have been described in these cases, and at least 2 cases (Ritchie and Case 3 above) of chorionepithelioma have been found.

Many writers lay but little stress on the value of the *x*-ray in the diagnosis of these cases unless the radiographs show the presence of bone or teeth in the tumor mass. The teratomata run a very chronic course and the comparison of radiographic plates taken at intervals of several weeks or months should help to lead to a correct conclusion in regard to them, irrespective of the exact interpretation of the radiographic shadows. The general spheroidal shape of the tumor mass, with smooth walls, the situation of the tumor, either in the anterior or posterior parts of the chest, should help to determine the nature of these cases. These tumors usually present no symptoms except those of the presence of a growth. There are no circulation symptoms, no thrills, no murmurs, no changes in the heart rhythm or in the blood-pressure, except as these may result from pressure symptoms.

The signs consist in the finding of an area of dulness with absence over it of breath sounds or of cardiac murmurs. The situation of the tumor may be anywhere in the chest, but including the dermoids they are usually found in the anterior mediastinum. It is possible that they will present externally in the episternal notch or cause a bulging of the sternum. In cases which become infected and rupture into a bronchus there would be an expectoration of cheesy pus which may contain hair. The pressure symptoms may cause a cough, a pain of moderate degree and a shortness of breath from pressure on the bronchi or on the lung. The *x*-ray will show a shadow of varying size indicating a more or less spheroidal mass which does not pulsate and which, after puberty, has a very slight tendency to increase in size.

The diagnosis is differentiated from the enlarged bronchial glands characteristic of Hodgkin's disease by the single tumor mass and the location, which may be in any part of the chest and is not necessarily central; from aneurysm, by the separation of the tumor from the bloodvessels, made possible through fluoroscopic examination, by the absence of pulsation and of murmurs over the tumor mass and by the comparatively more rapid growth of aneurysmal tumors; from pulmonary abscess and encysted empyema, by the location of the shadow, and except in infected dermoids by the absence of fever; from the hydatid echinococcus cyst by the slower

growth and the possible absence of a characteristic complement reaction in the blood; and from the metastatic malignant tumors, by the history of the case, the absence of a primary growth and by the different period of life when the tumor develops.

In the cases reported above, Case 1 is probably a teratoma because of its long duration without growth, of the deformity of development in the bodies of the four vertebræ in contact with the mass, of the continued good health of the patient, of the absence of circulatory signs in the tumor and of the freedom from pressure signs, which are absent because the surrounding organs have accommodated themselves to the presence of the tumor during the growth of the individual. Case 2 is more doubtful in its pathology. The differentiation from an aneurysm was considered justified because specific tests for syphilis did not develop even under provocative treatment and because the tumor mass had a peculiar and unusual spheroidal form and remained stationary during more than a period of two years. The patient died suddenly from a fatal syncope without internal hemorrhage, probably from nerve pressure. Case 3 was diagnosticated *ante mortem* as a teratoma because of the location, size and shape of the tumor shadow and its differentiation from aneurysm. The diagnosis was confirmed at autopsy. Case 4 presents a tumor of the anterior mediastinum in a young man, aged nineteen years, who has not passed beyond the age of growth and development. The mass has gradually increased in size during three years and has remained a smoothly spheroidal tumor which presupposes a cyst growing by an interior accumulation of semifluid contents. The diagnosis of a dermoid cyst seems quite justified. Case 5 appears to be a similar condition to that presented by Case 4. The location, the general contour of the shadow and the negative findings in physical signs would seem to warrant the diagnosis of a dermoid or teratoma. The subsequent history of fever, the discharge of an abscess cavity from the bronchi and the radiographic findings justify the further inference of an infected dermoid with rupture into a bronchus. One possible ending of such cases is shown in this patient, occurring after the usual period of growth is ended and due to a streptococcic infection of a dermoid cyst. Case 6 also presents the picture of a

teratoma or highly calcified dermoid in a patient aged fifty-four years. It has not been possible to take a second picture, but the health of the patient in March, 1920, is still good.

The treatment of these cases is entirely surgical and the results so far reported, which are given in detail below, show a very high mortality, as might be predicted from their nature.

None of the present series has been operated on, although it seems indicated with some urgency in Case 4. Cases 1 and 6 do not seem sufficiently inconvenienced by their tumors to warrant interference and Case 5 has run a course which may lead to a spontaneous cure. Cases 2 and 3 have died.

Histopathology. The microscopic examination of the tumor from E. J. B., or Case 3 above, shows that it is a very complex teratoid growth. The main part of the mass, which is soft, honeycombed with small cysts and relatively avascular, is composed of a very edematous stroma penetrated by ducts and irregular glandular structures. Some of these are sharply defined, with a firm basement membrane and a lining of well-preserved squamous epithelium. Others, also discrete, are lined with ciliated columnar epithelium. In one instance the two types are continuous, forming such an arrangement as appears normally in the nasal mucosa (Fig. 13). Throughout the stroma are a few hair follicles and sebaceous glands, but they form no large part of the structure, all cutaneous elements being rather scanty. Mature skin is not seen and the epithelial cysts are more often of the epidermoid type, filled with fluid and small quantities of keratin rather than with sebaceous material.

Numerous other epithelial structures are seen, many of them difficult to classify. There are long, irregular, glandular acini, some of them resembling intestinal mucosa (Fig. 13). The epithelium is anaplastic, and although these atypical forms raise the question of malignancy, such a diagnosis does not seem justifiable. The variations in arrangement of epithelium and stroma are due more to the inflammatory and degenerative changes in the tissues than to the proliferative tendencies of the cells. The columnar epithelium is found in one instance so associated with smooth muscle as to reproduce the appearance of a portion of the gastro-intestinal tract.

Other epithelium resembling ependyma is seen composed of evenly palisaded cells, with nuclei large and hyperchromatic, and so both in arrangement and form recalling the lining cells of the cerebral ventricles. Such a duct is seen in Fig. 14, surrounded by a loose reticular and infiltrated stroma. Pigmented tissue is present which resembles the choroid coat of the eye.

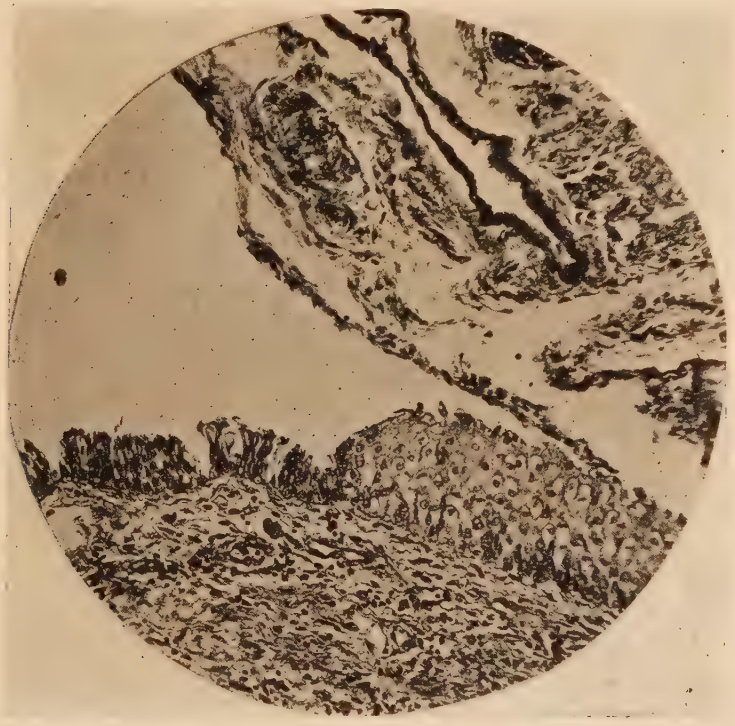

Fig. 13.—Duct lined with squamous and tall columnar epithelium.

A large part of the tumor consists of masses of neuro-epithelium, much of it arranged in the form of rosettes. These cells frequently surround a central area of glia and undoubtedly represent some abortive attempt to form a fetal brain. The glia is, as is usual in any complex dermoid, of a nearly normal type with small spherical nuclei and delicate ramifying offsets (Fig. 15).

In that portion of the mass which on section revealed calcified structures there were found many small fragments of bone and cartilage (Fig. 16). The smaller ossified areas show many osteoblasts and a thin layer of periosteum. The bone cells are practically normal. The cartilage shows only slight irregularities in the form and distribution of its cells and the staining reactions are normal.

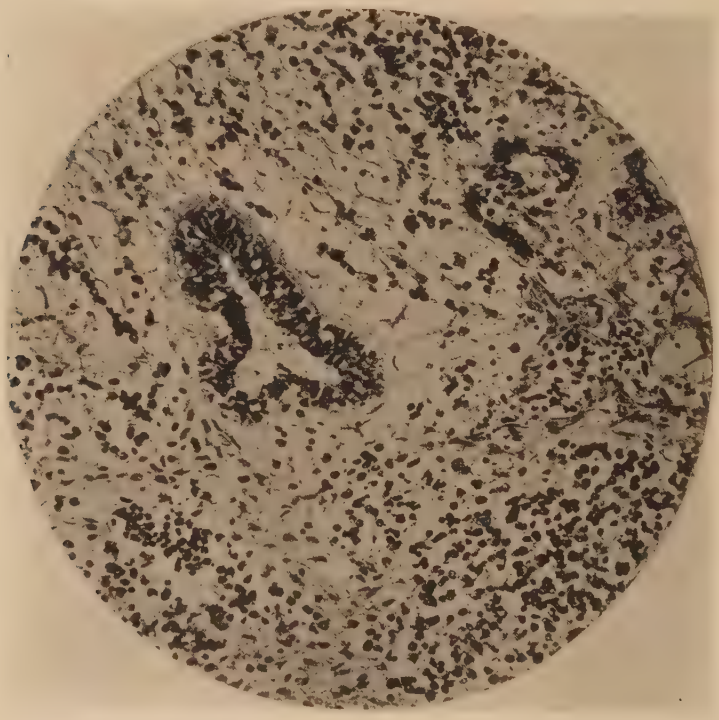

FIG. 14.—Duct with tall columnar epithelium suggesting ependyma.

The most interesting and apparently most actively proliferating structures are, however, those cell masses showing the morphology of a chorionepithelioma. These are seen chiefly in the anterior portion of the tumor, and they are the only cells present in any of the metastases. Such an area is readily located macroscopically

by associated hemorrhage, as it is composed largely of extensive vascular channels bordered and invaded by irregular cell groups. There is no stroma between the cells. Many cells of Langhans' type and smaller amounts of syncytium compose this part of the growth (Fig. 17). The former are variable in size, with relatively large vesicular nuclei and a well-defined cell membrane and

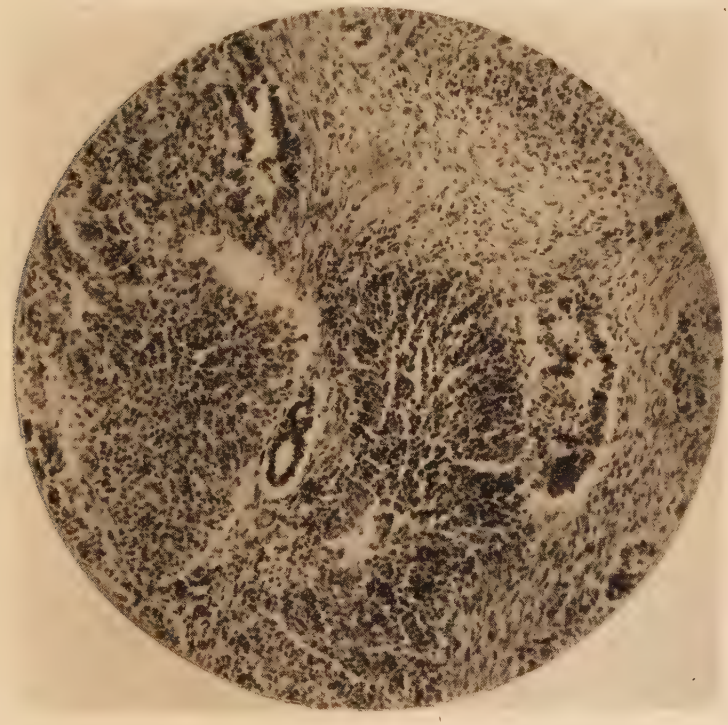

FIG. 15.—Masses of neuro-epithelium forming rosettes and ducts.

clear delicate cytoplasm. The syncytial masses are frequently very large, multinucleated and take the acid stain readily. Stereocilia are clearly shown, both on the free surface and also within lining large vacuoles (Fig. 18).

Several authors have described syncytial cells in these tumors apparently referring to occasional areas in which cell borders are

indistinguishable, but the morphology in this case is so clear cut and the histologic details so well preserved as to leave no room for doubt that these structures are exactly such as occur in the chorion-epitheliomata of pregnancy. The two cell forms are readily distinguishable both by outline and by their staining reactions.

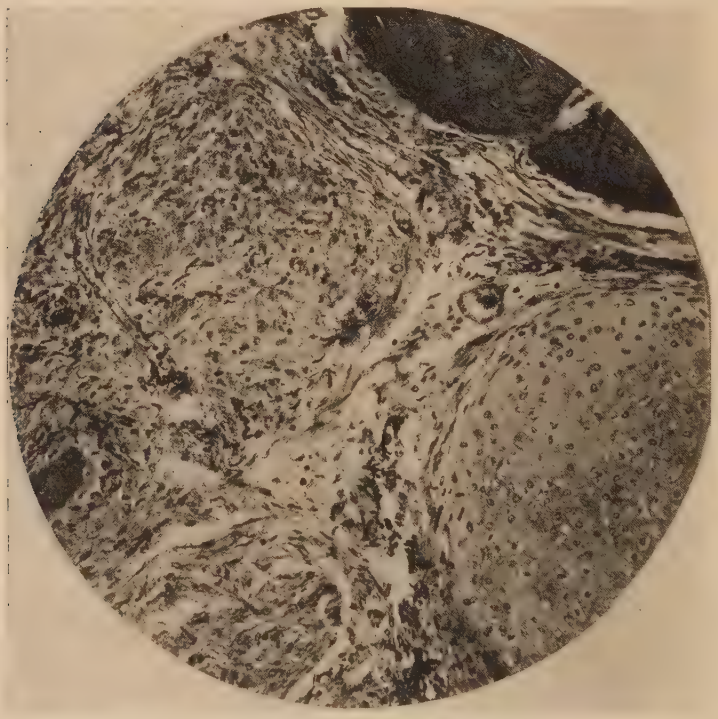

FIG. 16.—Areas of bone and cartilage.

The nodules in the lung and the one on the parietal pleura, the metastases in the bronchial nodes as well as those in the liver, reproduce all of these details perfectly. They show the gross as well as microscopic hemorrhage. The dilated vascular channels are blocked by tumor cells. The liver and lung are both being invaded and destroyed, and with very little encapsulation of the metastatic foci.

LITERATURE. The literature concerning mediastinal dermoids contains report of 79 cases, including the present. A summary of the cases was made in 1902 by Christian, who tabulated 40. Dangschaat, in the following year, published abstracts of 42 cases and added 2 more. A still more complete *résumé* of the literature was made by Morris in 1905, who included a number of cases not mentioned in the earlier reviews and added 1 of his own. As

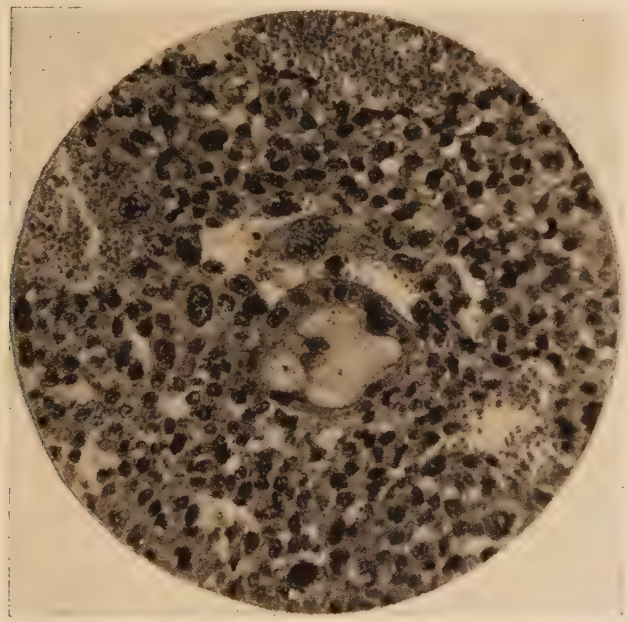

FIG. 17.—Areas of chorionepithelioma in liver metastasis, showing Langhans' cells and syncytium. × 200.

careful abstracts are given in his paper of all the 57 cases, with the exception of that of Warthin, reported up to that time, we have not reviewed these in detail. We have, however, given in detail a *résumé* of those which have appeared since. Hertzler, whose report is the last to summarize the subject, gives a bibliography of these cases also, but includes several which we do not enumerate, since the diagnoses do not appear to give sufficient

evidence as to the nature of the cyst in 4 of the cases. Others have been omitted because of duplication in the records.

The case of French was reported as a probably hydatid cyst rather than a dermoid. The roentgenogram shows a cystic tumor in the lung, but positive evidence to support either diagnosis is lacking. The case of Jones has been included in some of the

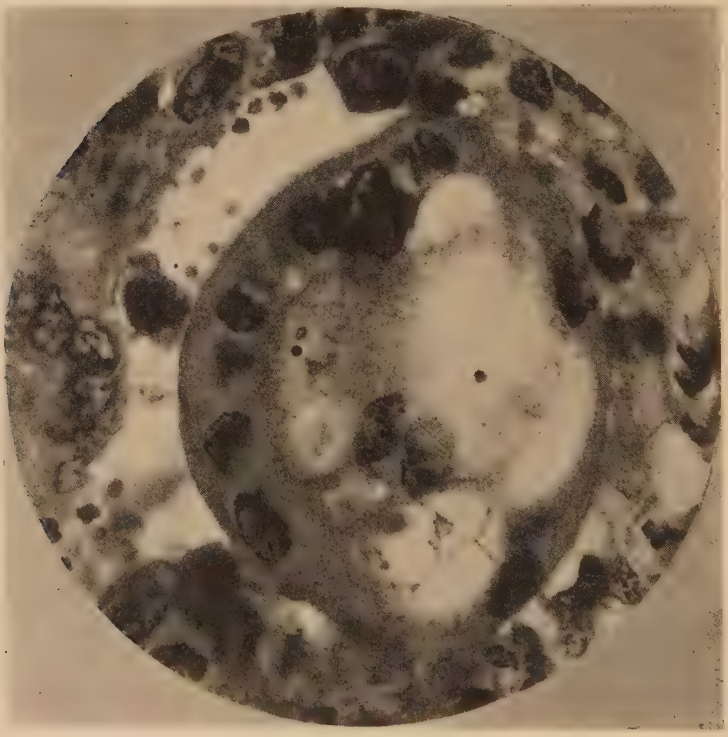

Fig. 18.—Details of syncytium from liver, showing stereocilia both on periphery and lining vacuoles. × 1000.

reviews, but it was reported very briefly and without sufficient data for diagnosis. Neither case was studied in detail for any considerable period of time. The case of Shaw is mentioned three times in the literature, being the same as that appearing under the name of Godlee and of Godlee and Williams. We have included it under the name of Shaw.

Spath gives a very interesting account of a large tumor appearing in the anterior mediastinum and extending into the neck, but thought to have originated in the fascia over the thoracic spine. It contained fibrous and fatty tissue, bone and cartilage, and has been classed with the dermoids by Pflanz and Dardignac. As no microscopic examination is recorded a precise conclusion as to its structure cannot be drawn.

The case of Lebert is thought to be the same as that of Naumann and those of Mohr and Münz are identical. Von Eiselsberg's first case is the same as Dangschaat's second and von Eiselsberg also reviews Türk's case upon which he operated. Renon's case was also reported twice.

Stilling found at autopsy a small cyst attached to the arch of the aorta; this was lined with ciliated epithelium, and although it showed bone, smooth muscle and mucous glands, it seems probable that it originated from misplaced cells of the entoderm of the respiratory or gastro-intestinal tract, either of which might be ciliated in the embryo. It would not necessarily be considered a true dermoid.

Data concerning Case 56, only mentioned by Morris, are given through the courtesy of Dr. Warthin, and will be fully reported by him later in a special volume concerning malignant blastomas of teratoid origin.

ABSTRACTS OF CASES

56. *Warthin.* Man. Aged twenty-six years. Laborer. Family history negative. Previous personal history negative until after lifting a hay-press. Thought he had "strained himself through the chest." Had pain in the chest for several days following this. This pain gradually increased, with symptoms of general indisposition, a slight fever, pulse 108, respiration 36, and when examined about four months after his first symptoms had developed he was found to have diminished expansion on the left side, with a great increase of heart dulness and very faint heart sounds. He had a constant, very dry cough, which was relieved by sitting up or by lying on the side, but increased on lying on the back. No friction sounds were heard; at this time he had no pain. A diagnosis of pericarditis with effusion was made. The area of cardiac dulness increased rapidly during the next few weeks with an increased dyspnea. Aspiration

of the pericardium was attempted and a small amount of bloody fluid was obtained. The patient's condition became progressively worse, and he died very suddenly. At autopsy a tumor the size of a child's head was found in the anterior mediastinum, outside the pericardial sac, and apparently springing from the tissues anterior to the great vessels. The main mass showed all the characteristics of a complex testicular or ovarian teratoid, cartilage, bone, rudimentary teeth, nervous tissue, a variety of epithelia, with very cellular areas in part sarcomatous in type and in part carcinomatous, with some syncytial formation. The entire pericardium and epicardium were covered with secondary carcinomatous nodules of epithelial type, some of these extending into the heart muscle. The important thing about this neoplasm is that it is exactly like the complex malignant teratomas of testis and ovary, located in the anterior mediastinum at the base of the heart and with carcinomatous metastases in the pericardial sac.

58. *Ritchie.* Man. Aged twenty-four years. Chief complaint: Pain in right chest and malaise for three days. Past history stated that he had not felt well for three months and had had hemoptyses for six weeks. There was a large area of dulness in the right chest. He became rapidly weaker, suffered severely from dyspnea and died of exhaustion. At autopsy there was found to be fluid in both pleural cavities. There was a mass in the anterior mediastinum which extended down over the pericardium. The tumor was in two parts: to the left a cyst 7 cm. in diameter, to the right a solid mass 15 x 12 x 6 cm. The cyst showed an irregular thin-walled cavity containing sebaceous material and hair. The solid part was continuous with this and composed of very vascular tissue. The tumor had metastasized into the lungs, liver and spleen, forming many spherical nodules from 0.5 to 5 cm. in diameter. Microscopically the cyst had a lining of squamous cells, with sebaceous glands and hair follicles in the wall. The solid tumor and metastases consisted of chorionepithelioma, with both Langhans' and syncytial cells.

59. *Shaw* (*same as Godlee and Williams*). Woman. Aged twenty-six years. Admitted to hospital June, 1905. Complained of severe cough and hemoptysis for three months. History of cough for eight or nine years and frequent expectoration of hair for seven or eight years. Had been treated for pleurisy at age of twelve years. Examination showed a prominence of the right chest with dulness from its apex to the fifth rib. Breath sounds were diminished or absent. Behind was less dulness; breath sounds, slightly diminished; no rales. Temperature below 99°. *X*-ray showed a shadow over the dull area. Operation January, 1906. Cyst was found at root of lung. Large amount of greasy, foul-smelling fluid evacuated. Large fleshy masses covered with hair projected into the cyst. Interior was cauterized. Condition improved. Patient

returned in May, 1906. Curetting and cauterization of the cyst was repeated ten times, with shrinking of the walls and reduction in size of the cavity. Cough and clubbing of fingers diminished. Wound remained, with foul-smelling discharge. Two of the pockets communicated with the bronchi.

60. *Carpenter.* Child. Aged two years. Chief complaint: Orthopnea; Rapid respiration and pain in side. Past history: For one year coughed and seemed languid. Pneumonia six months previously. On admission the patient was cyanosed. There was retraction of lower intercostal spaces and bulging of right chest. Right chest was dull throughout. Breath sounds were bronchial or absent on right and at left apex. Heart was displaced to the left. Temperature, 99°. Pulse, 136. Respiration, 60. Aspiration was done, removing 13 ounces of pale straw-colored fluid. Second aspiration showed bloody fluid. Condition improved. Returned to hospital soon after, cyanosed and moribund. Dulness had increased. Autopsy showed the pleuræ were normal. Right lung entirely compressed. In front of it was a cyst, the size of a fist, containing 6 to 8 ounces of clear fluid. Inside was cheesy material and hair. On section smaller cysts were found communicating with it and separated by fat, fibrous tissue and calcified area.

61. *Nordmann.* Man. Aged sixteen years. Patient demonstrated after operation. Chief complaint had been cough with dyspnea and pain in the side. Onset abrupt. Operation: Incision and drainage. Cyst had been found in the walls of which were cartilage and nerves. Sac could not be freed because of extent of adhesions.

62. *Renon.* Woman. Aged twenty-two years. Chief complaint: Severe dyspnea. History of dyspnea, slight at first, five years previously. Lately there had been intercostal pain at times and attacks of coughing, without expectoration and afternoon temperature. A puncture in the fourth space had shown a few drops of pus. On admission was orthopneic, with cyanosis of the lips, prominence of the jugulars, pulse rapid and small. Temperature normal. Deglutition was painful. Liver extended below the costal margin and was tender. Chest showed absence of fremitus in both lower lobes, with flatness and absent breath sounds. Exploration showed grumous yellowish-gray fluid containing amorphous material. Diagnosis of interlobar pleurisy. Symptoms grew worse; severe dyspnea threatened suffocation. Operation done under local anesthesia. Subperiosteal resection of eighth rib. Lung cavity was found, about 22 x 9 cm., containing sebaceous material. It was drained. Patient died two days later. Autopsy showed a large multilocular mass adjacent to the heart and attached to the diaphragm. It was pale gray, composed of communicating cysts, contained hair and much cartilage in the upper portion. Weight over 11 kilos. The cyst surrounded the great vessels and was

adherent to both lungs and to the pericardium. Trachea and aorta were not compressed. Microscopic examination showed squamous epithelium, fibrous tissue and skin glands, cartilage and bone and cubical and cylindrical epithelium. Thymic corpuscles were found in various parts of the cyst.

63. *Griffen.* Boy. Aged fifteen years. Past history irrelevant, but was thought never to have been strong. Complained of cough for five years without expectoration. Had had pain in the chest for eight months; was short of breath and voice was husky. The right chest was somewhat fuller than the left. The patient was pale and thin; there was dulness over the greater part of the right chest anteriorly; respiratory sounds were diminished and fremitus was absent. Diagnosis was made of encapsulated pleuritic effusion or growth. Aspiration showed thick dark green fluid with a few hairs. Resection of a rib was done, showing the large tumor mass. This also containined the same thick fluid. A subsequent operation was performed, with resection of several ribs; the mass was found to occupy nearly the entire right chest, and a large portion of it was excised. The cavity was packed. The patient failed slowly and died in two and a half months. During this time the tumor grew rapidly, causing much bulging of the chest wall. The material removed at operation showed a large grayish lobulated tumor of rather tough elastic consistency. It contained skin, cutaneous glands and many small cysts lined with cuboidal or cylindrical epithelium. There were also neuro-epithelial masses and neuroglia. The tumor was not thought to be one which would metastasize readily. No autopsy was obtainable.

64. *Mouat.* Boy. Aged seventeen years. Admitted to hospital October, 1908. Good health until one year previously. Cough in January, 1908. In April swelling of abdomen with edema of legs. On admission general edema and ascites. Tapped frequently, but both increased. Physical examination showed dulness extended about one inch each side of the manubrium and merged below with heart dulness. Breath sounds tubular, voice increased. Temperature, 100° to 101°. Died November 25. Autopsy showed a cyst adherent to diaphragm and continuous with the anterior wall of the pericardium, which was distended with purulent fluid, fat and long hairs. It communicated by a narrow neck, with a sac as large as an orange. No pericardial sac could be found. Heart was embedded in thick posterior wall of the cyst, which appeared to have grown from the pericardium or to have become completely adherent. There were extensive pleural adhesions. Viscera were congested but not diseased. Streptococci were cultured from cyst fluid. Cyst lined with scaly fat covered with integument and cavity constricted by broad fleshy band. Described in Godlee's paper, P. R. S. M., 1908–09.

65. *Becker and Carey.* Man. Chief complaint: Short of breath; pain in chest, more on left side; pain in abdomen. Duration about two weeks.

Physical examination showed a well-built and well-nourished man. Cyanosis. No respiratory movements on the left side; flatness on the left side anteriorly and below the spine of the scapula behind. Tenderness over the sternum. No breath sounds on the left. Egophony present. In ten days was much worse; slight temperature; dyspnea increasing. Three liters of fluid were removed, but it soon reaccumulated. An area of dulness from the second to the fourth rib was constant. Edema of the face and left arm developed. Autopsy showed a mass in the left chest, 30 x 20 x 10 cm., weighing 4300 gm., extending from the upper border of the sternum to the diaphragm, rather firm and encapsulated, but on section was hemorrhagic and apparently cellular. Liver showed numerous nodules about 1 cm. in diameter. Microscopically most of the tumor was of soft cellular connective tissue, showing a small amount of cartilage, with many cysts and glands lined with ciliated and squamous epithelium. Neuroglia was also found. Liver metastases were like tumor, except that no epidermis and no cartilage were present. No distinct blood supply was found. No epidermal structures in the liver.

66. *Kaestle.* Woman. Aged thirty years. For years suffered with pleurisy. For four weeks cough; many times coughed up hair. Showed signs of former pleurisy. *X*-ray showed a cyst attached to the pericardium and great vessels.

67. *Sieber.* Man. Aged sixteen years. Chief complaint: Dyspnea, cough and tachycardia. No symptoms until six months previous. Physical examination showed the whole of the left chest flat, with no breath sounds; the right was normal. Exploration of the back and left side showed thick jelly-like fluid. Microscopic examination showed squamous epithelium and keratinized scales. Operation: Incision and drainage. Death ten days later. Autopsy showed a large tumor in the anterior mediastinum between the pericardium and the lungs. It measured 22 x 19 x 11 cm. Both lungs were compressed and adherent to the tumor. The tumor was for the most part encapsulated, although at one point this fibrous sheath was almost lost where the tumor was growing into the lung. It consisted of a large cavity with rough walls into which nodular growths protruded. It was lined with squamous epithelium. There were bone and cartilage in small fragments, large venous sinuses and peripheral nerves. The greater part showed small cysts or glands lined with various types of epithelium, many squamous, others cylindrical, cuboidal or ciliated. Some showed papillomatous projections. There were small groups of mucous glands resembling duodenal glands and in other places part of the intestinal tract was distinguishable.

68. *Goebel and Ossig.* Patient complained of a fistula over the sternum, which he had had for a long time. There was pain in this region and to the right. Incision and drainage had been done a few weeks earlier.

Operated again, both pleural cavities being opened. A cyst 8 cm. in diameter was found which contained hair. Microscopically it contained cutaneous epithelium, with skin glands, smooth and striated muscle and partially formed glands resembling salivary glands.

69. *Ceelen.* Man. Aged thirty-three years. Diagnosis: Mediastinal sarcoma; pleurisy. Examination showed right chest dull. Breath sounds bronchial or absent. Aspiration was done with removal of 1200 c.c. of fluid. Death in one month. Autopsy showed on opening the thoracic musculature nodules of the tumor on the left side over the first and second ribs. There was hemorrhagic exudate in the pleuræ. A mediastinal carcinoma was found growing in the wall of a dermoid cyst about 10 cm. in diameter. It was attached to the sternum, compressed the left subclavian vein and partially compressed the trachea. Metastases into the cervical and bronchial nodes, lung, pleura and liver had occurred. Microscopic examination revealed skin, sweat-glands, smooth muscle, cartilage and cysts lined with cuboidal epithelium, so as to resemble thyroid. Bloodvessels and nerves were found. Carcinomatous tissue with the formation of parts of glands was seen. The metastases showed these glandular arrangements, except the growth on the chest wall, which was apparently of squamous epithelium, although no pearls nor keratinized areas were seen.

70. *Schutt.* Man. Aged nineteen years. Chief complaint: Swelling of face, cough, pain in the chest and dyspnea. Total duration four weeks. There was marked swelling and cyanosis of the face, arms, neck and upper chest. Breathing was stertorous. There was a large area of dulness in the right chest anteriorly extending down to the heart dulness and a smaller one on the left. *X*-ray examination showed a shadow the size of a child's head, with sharp outlines overlapping the large vessels and part of the heart. There were no pulsations and the heart was of normal size. Dyspnea and cyanosis increased and death occurred in four days. Autopsy showed a tumor 17 x 11 x 12 cm., solid on the left side, more soft and hemorrhagic on the right side with implantations on the lung. The vena cava was constricted and the right subclavian and innominate thrombosed. The pericardium was invaded and nodules protruded into the interior. Microscopically the tumor is a solid mixed tumor, with cartilage, epithelial cysts, smooth muscle and cellular areas resembling the prickle cells seen in mixed tumors of the salivary glands as well as cylindrical cells. Both types have characteristics of malignancy and form alveolar sarcoma and adenocarcinoma, both invading the bloodvessels.

71. *Prym.* Girl. Aged sixteen years. Protrusion of several ribs in the anterior thoracic region. Exploration showed clear fluid with a few cells. Operation was done a few months later, with resection of a rib. Clear fluid mixed with epithelium and hair was obtained; eight months

later operation again with resection of several ribs. The cyst was exposed, but was too adherent to be extirpated. Discharge from the wound was profuse for three months, when it diminished. A dermoid growth about 2 cm. in diameter appeared on the edge of the wound. This increased in size. A third operation was done, resecting the third to the seventh ribs. The tumor, covered with epithelium, was exposed, with heavy projections 2 to 3 cm. in diameter. One contained hair. A portion 7 x 3 cm. was excised. A calcified portion contained teeth of different varieties. Microscopic examination showed hair and skin glands, central nervous system with calcification, glia, bone, fatty marrow, squamous epithelium, thyroid (?), mucous glands, tall epithelium resembling nasal epithelium, nerves, smooth muscle.

72. *Hertzler.* Woman. Aged twenty-three years. First suffered from difficult respiration and fulness in the neck. Dulness over the upper region and for 2 cm. above where the mass was visible and palpable. Operation was done, removing as much of the sac as possible. Patient rapidly recovered. The tumor was about the size of a walnut, lined with epidermis which was studded with small hairs. Microscopic examination showed sweat and sudoriferous glands.

73. *Hamman.* Man. Aged thirty years. Admitted to the hospital in 1914. Chief complaint: Cough and expectoration. Past history: Asthma at six years. Four years before admission had cold and pneumonia in three successive years. Severe dyspnea and eventually hemoptysis, which had continued at intervals. Was diagnosed as tuberculous and sent to Colorado. On admission the right chest was normal. Fulness and diminished movement on the left. Dulness becoming flatness below, extending from the apex to the fourth rib. Breath sounds diminished. Breath and voice sounds bronchial. Sputum showed elastic tissue; no tubercle bacilli. In 1916 noted hairs in sputum.

74. *Black and Black.* Man, aged forty-six years. Admitted 1915. Chief complaint: Soreness of left chest, cough and dyspnea. These were attributed to the result of a blow from a falling tree received ten months previously. Chest showed diminished respiration on left anteriorly. No venous engorgement, edema or deformity. Resonant anteriorly, but in fifth to eighth spaces posteriorly dulness and absent breath sounds. Right chest clear. Aspiration showed 30 c.c. of bloody fluid. *X*-ray showed large shadow on the left side. Symptoms became worse. Operation: Resection of the sixth and seventh ribs posteriorly. Pleura bulged and pulsated. It was stitched to the lung and cauterized between stitches. Fluid exuded. Interior was explored with the finger and cheesy material removed. Drainage. Improvement for one month, at which time exudate increased. Chills and fever supervened; cough and pain became more severe and hemoptysis occurred. Died in December with severe

hemoptysis. Sections of tissue removed at operation showed teratoma with a few carcinomatous areas.

75. *Harris.* Woman. Aged nineteen years. Russian. Chief complaint: Dyspnea and weakness. The *x*-ray showed a shadow in the right chest and hairs were obtained by exploratory puncture. Operation was performed, disclosing a growth which occupied the greater part of the right pleural cavity and was adherent to the diaphragm, pericardium and root of the lung. It was a cyst 22 x 19 x 10 cm., lined with fatty material and hair. There were four other small dermoids, only one of which communicated with the main cyst. The mass weighed 2800 gm. Owing to the fact that the collapsed right lung failed to expand it became necessary to obliterate the right thoracic cavity. The patient then made a complete recovery.

76. *Staffieri.* Woman. Aged thirty-three years. Chief complaint was pain in the right chest, hemoptysis and cough. These symptoms had persisted for seven years, and for two there had been an expectoration of hair. An operation was performed followed by rapid recovery, except for a small fistula.

77. *Kleinschmidt* (2 cases).

Case 1.—Male. Aged seventeen years. Chief compaint: Sharp pain in right chest, intermittent for eight months, becoming more severe. Examination showed face cyanosed; veins of the right chest, neck and face dilated. Right chest wall anteriorly below second rib was flat. *X*-ray examination showed a sharply circumscribed shadow in the lower and middle part of the right lung, merging with the heart shadow but moving with respiration. Ribs were resected in the scapular line and pus evacuated. Two months later the fourth rib was resected anteriorly, disclosing dermoid. Drainage for four weeks following and finally a radical operation was performed. The tumor was the size of a goose egg, nodular inside. Two subsequent operations were done to obliterate the cavity and in a year the patient was virtually cured. The tumor contained skin, skin glands, hair and cartilage and smooth muscle, nerve tissue, columnar epithelium. There were also glandular structures resembling pancreas, with islands of Langerhans and salivary gland.

78. Case 2.—Female. Aged twenty-four years. Chief complaint: Pain in the chest for two years. Dyspnea and dysphagia six months. Examination showed the whole thoracic wall bulged forward. There is marked pulsation near the sternum, but not spreading diffusely and no bruits or murmurs. *X*-ray showed a tumor of the left chest. Radical operation was performed through the anterior incision. Both pleural cavities were opened but the course and healing were rapid. The tumor measured 15 x 10 x 10 cm. and weighed 850 gm. One sac was lined with

epidermis with hairy outgrowths; other parts showed small cystic cavities lined with ciliated epithelium. The walls contained also cartilage, bone, smooth muscle and nerves.

79. Case 3 is the only one in this report concerning which the diagnosis has been confirmed by autopsy. It alone is included in the following pathologic survey:

These 79 cases fall roughly into three groups: First, the simple dermoids in which only a single cyst is found, evidently of ectodermal origin, usually lined with squamous epithelium, and containing within its walls a variable number of specialized epidermal structures, as teeth, hair, sweat and sebaceous glands. These form the majority of this group of tumors, 58 per cent. having shown only such structures.

The others have shown tissue derived from mesoderm or even well-formed organs in which all of the germ layers are represented. Bone, cartilage, smooth and striated muscle are found most frequently, while structures resembling respiratory and gastro-intestinal tract, cysts with columnar or ciliated epithelium and various forms of nervous tissue, as ganglia, glia and embryonic brain, have occurred many times. More rarely portions of an eye with pigmented choroidal tissue and a few times thyroid gland have been identified. Such complex tumors may or may not be associated with a single large cyst which forms the main bulk of the growth. More frequently such is the case, though the dimensions of the cyst have varied from 3 or 4 cm., as in the case of Salmonsen, to a very large single or multilocular sac occupying practically the whole of one of the pleural cavities and measuring 25 to 30 cm. in length. The cases of Sieber, Renon and Sangalli illustrate this type of growth. The tumors of Fofanow and of Griffin showed many small cysts giving a honeycombed appearance to the entire structure but no single large one.

The third and smallest group of these teratoid tumors has shown one or in some cases two forms of malignancy, besides a variety of tissues and cellular material. Of the entire series 9, or 11 per cent., have exhibited both the morphology and the behavior of such teratomata, resembling in every way these tumors as they occur in other parts of the body, especially the ovary and testis. As in the second group a solitary cyst of considerable size has

usually been found in some part of the tumor, with the exception of the cases of Warthin, possibly von Eiselsberg, and in the present case. There has been considerable variation in the development of the malignant tissue, and as we are dealing with such a case, we review again those belonging to this group:

Virchow, in 1871, described a large mediastinal tumor in a young man. It contained a small cyst, 1.5 to 2.5 cm. in diameter, and showed tissues resembling fetal lung with elastic fibers and portions of the intestinal tract. Spindle-cell sarcoma formed a considerable portion of the growth and a nodule on the rib was carcinomatous. These structures had metastasized.

Pinder's tumor comprised both a fair-sized dermoid cyst and a cellular tumor, with the morphology of a small round-cell sarcoma which was invading the lung.

Jores found both a large cyst with squamous epithelial lining and an extensive cellular neoplasm composed in part of spindle-cell sarcoma nearly filling the left pleural cavity. Cylindrical, cuboidal and ciliated epithelium were present, also cartilage, smooth muscle and cutaneous structures, as teeth and skin glands.

The pathologic findings in the case of von Eiselsberg (occurring in an infant) are stated only as showing a "dermoid attached to the lung and compressing it. Microscopically it showed sarcomatous degeneration of a teratoma of bigeminal origin in which bone and cartilage developed."

Ritchie's case is of considerable importance in connection with the present one, as it alone shows the same manifestations of malignancy—that is, typical chorionepithelioma—both in the primary tumor and in the metastases in the liver and spleen. It will be noted that besides a cyst there was a large, solid, hemorrhagic mass showing both Langhans' cells and syncytium.

Warthin describes a blastoma in which there are areas of sarcoma and again of carcinoma, with some syncytial formation. The metastases were carcinomatous.

The tumor of Black and Black probably contained a cyst which was opened at operation. A portion of the wall showed carcinomatous areas.

Both alveolar sarcoma and adenocarcinoma were observed by

Schutt in the primary tumor of his patient, and both these structures had metastasized.

The fact that two types of malignant tissues have been described in each of three cases is merely an indication of the embryonal and incomplete differentiation of the cellular elements rendering impossible clear distinctions between the epithelial and mesothelial forms and relations with which we are familiar in more mature tissues.

TREATMENT. Surgical interference has been attempted in about one-third of the cases, either in the very mild ones presenting a fistula and a small cyst which could be extirpated without seriously embarrassing the heart or respiration or else in the severe cases in which pressure symptoms were very distressing. The operative procedures and results have been as follows:

Case.	Condition.	Operation.	Results.
Pöhn	Large pulsating tumor	Incision	Diminished in size; no statement as to outcome.
Küchman	Large tumor pointing in neck	Incision	Improved.
Godlee	Swelling in axilla	Marsupialization; resection of ribs	Cough diminished; results fair; lived four years.
Koenig	.....	Incision; resection of sternum	Fistula.
Koerte	Discharging sinus of chest wall	Resection of ribs and sternum; cauterization	Secretion less; died of tuberculosis.
Bastianelli	Sinus following earlier operation	Complete extirpation	Cured.
Dardignac	Tumor of right chest visible	Incision; cauterization of cyst	Much improved but fistula remained.
Pflanz	Fluctuating tumor at sternoclavicular articulation	Resection of sternum; cauterization of cyst	Fistula remained; much improved in four months.
Bergmann	Fistula in middle sternum and bulging of ribs	Resection of ribs and complete removal	Improved; in four months the wound nearly healed.
Greishammer	Dyspnea and pain	Resection of portion of cyst; marsupialization.	Improvement.
Mandelbaum	Bulging on right chest wall; no signs of compression	Excision of extra thoracic portion and drainage	Death in six weeks.
von Török	Abscess of back and carious ribs for three years	Extirpation	Died in three weeks.

Case.	Condition.	Operation.	Results.
Foucher . .	Right chest bulging	Resection of rib and drainage	Partial recovery.
Dangschaat .	Chest bulging	Incision and drainage	Improved; lived two years.
Dangschaat .	.....	Incision and drainage; marsupialized	Died in ten days.
Predschenski	.....	Drainage; resection of rib	Improved.
Madelung .	Visible tumor of right chest	Incision and drainage	Improved; lived six years.
Madelung .	Pleurisy and cough	Resection of ribs and total extirpation of cyst	Complete recovery.
Türk . . .	Cough and dyspnea	Resection of ribs and extirpation of sac	Cured.
Shostak . .	Tumor in jugular notch	Incision and drainage	Died in a few days.
Nordmann .	Cough, dyspnea and pain	Incision and drainage	Improved.
Renon. . .	Dyspnea and cyanosis	Resection of rib; drainage	Death in two days.
Griffin . .	Right chest prominent; dyspnea, etc.	Resection of rib and drainage; partial extirpation	Died two months after second operation.
Shaw . . .	Prominent right chest; cough; hemoptysis	Incision and drainage (ten times)	Fistula; improved.
Sieber . .	Dyspnea and cough	Incision and drainage	Died in ten days.
Prym . . .	Prominence of ribs	(3) resection of ribs	Improved; fistula; seen one year later.
Black & Black	Cough and dyspnea	Resection and drainage	Hemoptysis; died in six months.
Harris . .	Dyspnea and weakness	Complete extirpation	Recovery.
Staffieri . .	Pain, cough, hemoptysis and expectoration of hair	Removal	Recovery rapid, but small fistula.
Kleinschmidt (1)	Pain, venous engorgement, cyanosis	Removal	Very small fistula, end of one year.
Kleinschmidt (2)	Pain, dyspnea and dysphagia	Removal	Cured.

It will be seen from this summary that incision with or without resection of ribs or sternum and cauterization of the cyst lining has been done eighteen times; Godlee, Greishammer and Dangschaat each dealing with a very large cavity, sutured its wall to the external skin surface. Two of these cases showed permanent improvement. Probably about 50 per cent. of the patients operated on have shown improvement following the simpler operations, while the total mortality has been about 27 per cent. A few

patients, those of Bastianelli, Madelung (2), Türk, Harris, Staffieri and both of Kleinschmidt's, were practically cured.

A further discussion of the surgical treatment will be found in the papers of von Eiselsberg who operated upon two cases and of Küchman, Madelung, Shaw and Kleinschmidt.

Discussion. These mediastinal tumors do not differ in morphology or behavior from those of similar structure occurring elsewhere. Wilms in his comprehensive discussion of the subject enumerates a considerable number found in the skull, cervical region, mediastinum, abdomen and sacral region, besides the much larger group found in the sex glands.

The brain teratomata, of which there are about 12 cases, were collected by Barron in 1916. They have varied in size from that of a walnut to an apple, are more frequent in the region of the epiphysis and have shown every indication of malignancy. It is of interest to us to note that the tumor of Askanasy and that of Rohdenburg, believed to be primary in the pineal, showed chorion-epithelioma.

In the neck, especially near the thyroid, such cysts and complex growths have also been reported. Ehlers, Kolisko and others have each described such tumors which were seen in infants and caused their death within a short time. They were composed of primitive neuro-epithelial masses and epithelial cysts.

Teratomata of the abdomen, both intra- and extraperitoneal, and without any evidence of connection with the reproductive organs, have been noted a few times. In an excellent paper by Montgomery there will be found an interesting report of a highly malignant intra-abdominal teratoma found at operation upon a child, aged twelve years. There is here a full discussion and comparison of the other abdominal cases mentioned in the earlier literature.

For the complex malignant tumors the sacral region is not a common locality. Czerny described such a teratoma containing squamous-cell epithelioma which showed direct transitions from this to ciliated columnar epithelium. It was quiescent for nine years but recurred after operation. The tumor also contained bone and cartilage.

Chorionepitheliomata of the testis have numbered 70, and are

collected by Woglom, in whose paper a discussion of their histogenesis will also be found.

The various theories that have been advanced in explanation of the origin of this mediastinal class of tumors have been so frequently and adequately discussed in the literature that we merely mention them here. The simple cysts were at first explained as derivatives of the ectoderm of one of the branchial arches, formed in the cervical region and later migrating into the thorax. Collenberg advanced this view because in his case there was found to be a band of tissue connecting the upper end of the cyst with the lower part of the thyroid. The vascular supply was derived from the inferior thyroid artery, and a thin strip of the gland was included.

Marchand who found a cyst closely associated with the thymus, at first inclined also to the view that their origin might be from ectodermal rests in that gland, but pointed out that a derivation from the lateral anlagen of the thyroid derived from the fourth branchial arch was quite as possible. Pinders from the close relationship existing between his cyst and the thymus, regarded this as the correct interpretation and deduced an ectodermal origin for the thymus. Virchow in explaining the various entodermal structures, regarded them all as embryonal rests that are separated in the closure of the thorax, both ectodermal and entodermal tissues being included. Thus the tubules resembling bronchi are explained not as an attempt to form fetal organs so much as a more or less accidental juxtaposition of respiratory epithelium with cartilage and smooth muscle. Wilms thought that the more complex thoracic growths, as Virchow's, are to be considered developments from small congenital rests set aside from the germinal layers at an early period.

Adami has also explained many of the sacral and cerebral groups as derived from local overgrowths of exuberant tissues produced by proliferation at the extremities of the primitive streak. Such an explanation is perfectly feasible for some tumors, and like the earlier explanations of the thoracic dermoids, is quite adequate for many cases.

Of late, however, the tendency has been to look beyond any one anatomic group and search for an explanation which shall apply

to all of them. As more of the complex tumors are found, one realizes the need of broader and more fundamental theories to replace the idea of mere local malformation. Any theory which will satisfy all the conditions involved in the genesis and development of these congenital tumors must take cognizance of and explain the following facts and undetermined relationships. One must consider the inferences to be drawn both from the relative frequency of occurrence of the teratomata in connection with the sex glands, for it is certain that teratomata of the sex glands both in male and female are more common than in other locations and also from the universal intimate relation of these tumors to the mid-line of the body. And, finally, one cannot overlook the greater incidence of that rarest form of malignancy—chorionepithelioma, in the tumors of the ovary and testis, and also the relation to the sex glands and to the fetus, of the tumor cells of chorionepithelioma found in a primary tumor in various parts of the body both in male and female subjects. Chorionepithelioma is in every case merely fetal ectoderm, and theoretically there is no reason why it cannot be produced from one totipotent cell as well as from another. Four theories have been suggested to explain the origin of the causal totipotent cell and the genesis of the teratomata.

It has been repeatedly shown in the lower animals, for example by Wilson, that if the segmenting ovum is stimulated at the two-cell stage by shaking in solutions of varying tonicity that the blastomeres may be isolated and caused to undergo cleavage with the formation of two small but otherwise normal embryos. Interference at the four-cell stage may result in two, three or four embryos, according to circumstances.

Morgan has also shown that alteration of position of a frog's egg at the two-cell stage caused each ovum to give rise to either two complete but half-sized embryos or two half-embryos. For tumors occurring outside the sex glands it therefore seems easy to suppose that some disturbance in physicochemical relationships occurring during the early stage of the fertilized ovum might readily result in some such process, but with subsequent inclusion and overgrowth of the embryonal structures which are destined to be the host. It is also easy to conceive of such a cell mass again

becoming attached to the host, implanting itself along the median line and being buried during the closure of the thorax or abdomen. That such a group of cells are totipotent and therefore capable of forming tissues or organs characteristic of any life-period is plain. It seems even strange that the trophoblast, which is differentiated rather early, does not more often appear in neoplasms. The chorionic epithelium is in this manner readily seen to be a part of the individual himself and so to differ in derivation if not in form from the chorionic epithelium which results during adult life of the female from fetal development during a pregnancy.

That such a process actually does occur in the higher mammals cannot be demonstrated, but on theoretic grounds it offers a feasible explanation for certain tumor forms. Anatomically there are many transition forms lacking between these complex tridermal tumors containing only rudimentary organs and the double monsters of nearly complete and independent development. A tumor which remains small and quiescent throughout the growing period of the host and then begins active proliferation might well be supposed to have a different origin from a twin which reaches mature cellular and organoid structure during embryonic and fetal life and which afterward is controlled by the same growth limitations as its duplicate. For such tumors the blastomere theory seems most feasible.

As a second explanation of the genesis a development from polar bodies cannot be denied. The nuclear chromatin extruded from the ovum during maturation is usually believed to be lost so far as the vital processes of the segmenting ovum are concerned. It would at first appear that any portion of the original nuclear chromatin might have potentialities for extensive growth. But even in mollusks, in which abnormal growth has apparently been stimulated by centrifugalization and other means, causing a giant polar body, there still seems quantitatively and probably also qualitatively an insufficiency of energy. No growth beyond the gastrula stage has ever been observed even in invertebrates, according to Doncaster. Even if fertilization of the polar body may rarely occur in mammals, to assume that it is the starting-point of a tumor, remains a highly theoretical proposition.

The third theory, and one which is by many held as most reason-

able, is to view all these complex neoplasms as fetal inclusions. Adami considers that such tumors may be true coeval twins, that is, developed from two independently fertilized ova, the one forming the host or autosite for the second which becomes parasitic. Homologous twins are, however, derived from two anlagen which develop from one ovum, and it is a parasite of this type which is most generally believed to be represented in the tumor mass of a teratoma. Many monsters and anomalies are unquestionably of this type, including the thoracopagi, to which the thoracic teratomata would, of course, be most closely related. This theory of origin from a second embryonal area, whether from one ovum or from two, is capable of explaining the origin of all the teratomata in as satisfactory a manner as does the theory of origin from a blastomere cell. Both theories seem more satisfactory than the third which ascribes their origin to a polar body.

The question of the relation of the germ cells themselves to these tumors is equally interesting. The much greater frequency of the teratomata within the ovary and testis than in any other location challenges an explanation. Many writers, as Marchand and Bonnet, believing that there are special early-differentiated germinal blastomeres and that their abnormal development may form differentiated cells, regard these as the source of such tumors. Others adhere to the theory that the sex cells themselves may undergo parthenogenetic development, even to the point of forming special tissues, such as Loeb has shown occurs in guinea-pigs. This writer has observed cells resembling chorionepithelioma within the unfertilized ova of his animals. Such a process might in a few cases even account for the development of these tumors in the abdomen and thorax if it were true of mammals, as has been observed by Beard in certain fishes, that sex cells are found at times in various positions in the embryo and are by no means limited to the sex glands. These sex cells, of course, are the isolated germ cells referred to by many writers, but like the polar bodies their persistence and growth capacities are unknown factors. At present there is a general tendency to draw a distinction between the origin of these tumors occurring in the sex glands and of those occurring elsewhere.

SUMMARY. 1. Mediastinal dermoid cysts or the more complex teratomata are infrequent tumors, but may occasionally be diagnosticated ante mortem. The roentgenographic findings are of great aid in diagnosis.

2. Symptoms due to pressure usually occur either in early childhood or during the second and third decades of life.

3. Eleven per cent. of the 79 undoubted cases reported have developed malignant characteristics.

4. Surgical interference has proved of benefit in about one-half of the selected cases, with an operative mortality of about 27 per cent.

5. No sharp line can be drawn histogenetically between the simpler cystic tumors and the complex and malignant ones. The latter are usually regarded as an inclusion of a retrograde twin fetus, but other sources cannot be excluded. These theories explanatory of their genesis include a growth from isolated blastomeres, from polar bodies and from a parthenogenetic development of sex cells. The simpler cyst may in some cases arise from embryonic remnants derived from one or more of the germ layers.

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DISCUSSION

Dr. J. B. Herrick, of Chicago, said that his autopsy studies were made on the patient who was followed for over a year. Fluoroscopic examination indicated there was no aneurysm. It was thought there was a dilated right auricle. The tumor was more attached to the pericardium than to the auricle. It was semi-solid and filled with cholesterin crystals. Such tumors within the pericardium were very rare.

Dr. Hobart A. Hare, of Philadelphia, asked if Dr. Lambert excluded ecchinococcus infection by the complement-fixation test. The spherical cysts were usually quiescent.

Dr. Canby Robinson, of St. Louis, said he noted there were 8 ounces of pus. Was there anything to confirm the diagnosis of teratoma? Some aneurysms produced no physical signs. He had shown a considerable number of plates of wired aneurysm. There was a very irregular outline in some of the plates which helped in the diagnosis. This fluoroscopic irregularity differentiated tumor from aneurysm. He had collected statistics as to mediastinal growths and found that dermoid cysts were rare, according to the literature. One should pay more attention to the mediastinal contents. He had been surprised to find how many cases came to the dissecting room. Most extraordinary changes could be found with reference to the peribronchial lymph nodes. Many fevers might be due to secondary suppurative changes in tumor formation. These were overlooked very often, and in any cases of unexplained fever one should think of the mediastinal lymph nodes. Many workers paid no attention to these tissues.

Dr. Samuel Lambert, of New York (closing), said that he had read of one case of dermoid cyst within the pericardium. Tests were not made in these cases by the complement-fixation method for echinococcus. He did not believe these cases of congenital tumors were quiescent, as Dr. Hare had said. In the case of abscess no hair was discovered in the discharged pus. The pus was examined very carefully. In regard to the possibility of aneurysm, fluoroscopic tests did not show any evidence of aneurysm in these cases. All the cases had a negative Wassermann. Some had been given provocative treatment, with salvarsan, in the endeavor to bring out this point and had failed in all cases. The diagnosis had seemed established by exclusion in all six and by autopsy in one of them.

THE PNEUMOPHONOGRAPH: AN ATTEMPT TO RECORD SOUND WAVES IN PHYSICAL EXAMINATION

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Determination of the physical condition of normal and abnormal lungs by their influence on the production and transmission of sound waves in the chest has not made much progress since its discovery.

Its use in diagnosis and prognosis may be divided for discussion into three parts:

1. The sound producer.
2. The medium.
3. The sound receiver.

The medium is the object of the investigation, the tissues, fluids and other contents of the chest, and is therefore not subject to improvement. Improvement in the methods may be sought only in the source of sound, when artificial, and in the receiver. These can both be modified and it is possible that the proper modification of these parts may increase our ability to determine the character and condition of the medium.

The sounds that have been used most commonly in the past are: (1) The sounds produced by the patients in inspiration and expiration; (2) the whispered and spoken voice of the patient; (3) cough; (4) percussion; (5) certain sounds of variable nature known as rales; (6) sounds produced by friction.

The sounds produced voluntarily or involuntarily by the patient vary so much in repetition that they cannot be used as the basis of exact measurements. Percussion and other artifically-produced sounds can be made much more accurate in repetition. The characteristics to be sought are constant intensity and ease of application to the desired portions of the body. Experiments have been begun with an artificial percussor and a vibrating telephone diaphragm. The former is so constructed that a spring dynamom-

eter indicates the pressure exerted against the body, which can therefore be made constant. By turning a small crank the hammer is raised against a spring and released at a definite point so that all taps are alike. This instrument so far has been found unsatisfactory, partly on account of the sounds produced by the mechanism.

The telephone diaphragm can be operated at convenient frequencies and intensities, by means of a high frequency alternator or an oscillating vacuum tube circuit. This source may be placed at the open mouth and the sound observed at different positions on the chest wall or *vice versa*, and may be used together with the receiving instruments described below. Variations in pitch, quality and intensity of sound are readily obtained by the use of the oscillating telephone diaphragm.

The receiver has almost invariably been the human ear, aided by the stethoscope. This has the following disadvantages: first, the sounds heard and their interpretation depend on the skill and the physical condition of the observer; second, the only record is the observer's translation of his observations into words, which do not convey the same idea to different readers; third, the human mechanism tires readily and in times of emergency, such as recruiting an army, fails seriously on this account; fourth, without the knowledge furnished by auscultation or its equivalent in pulmonary conditions we are robbed of an exceedingly valuable, if not the most valuable, aid in some phases of diagnosis, prognosis and treatment.

The preliminary work on the sound receiver, although revealing a great many difficulties, still holds out the hope of some type of pneumophonograph laboratory where permanent records of at least the sound conduction of a patient's chest and its contents may be produced by an untiring instrument.

The instrument that has been used in these preliminary tests consists of a microphone developed by the Western Electric Company for stethoscope work and kindly loaned to us for this investigation, a hindle string galvanometer and camera with the necessary accessories of lenses, rheostats, batteries and transformers. The records obtained are illustrated by the accompanying reproductions.

These records present for study the three fundamental characteristics of the sound: namely, intensity, pitch and quality. The intensity is indicated by the amplitude or width of the swing. The

amplitude is determined by the sensitivity of the instrument and the intensity of the wound. The sensitivity may be varied in several ways and may be determined, so that records taken at different times may be compared. Pitch is determined by the number of vibrations per second and indicated by the number of swings in the corresponding interval on the record. Quality depends on the relative frequencies and the relative intensities of the component vibrations and is indicated by the shape of the curve. All these are illustrated in the accompanying figures.

The intensity and pitch sounds are easily determined from the records. The recognition of a definite quality or type of sound, however, is a more difficult task. As shown in the curves, the shapes corresponding to different sounds are quite noticeably different, so that the recognition of pathological sounds from the shapes of the curves may not be impossible. One difficulty is encountered in the fact that the instrument records all sounds of sufficient intensity. In auscultation the attention is possibly fixed on one particular sound or type of sound and the rest are not heard. In this case muscle sounds, skin sounds, involuntary motions of the hand that holds the stethoscope bell, etc., are all recorded, so that the analysis is not simple. By special precautions some of these sounds may be eliminated. Others may possibly be filtered out. In order that complex sounds may be recorded with their true characteristics, it is important to choose carefully the constants of all vibrating parts, especially the diaphragm, air columns, and the string. It may be possible to use filters so as to record only certain definite determining frequencies.

For study of the transmission of loud, artificially produced sounds of a definite frequency, such as that described above in the case of the telephone diaphragm, it is possible to use a simple indicating instrument, since the only property involved is the intensity. This will be attempted in the following manner: The electric current produced in the microphone will be amplified, rectified, and read on a direct current galvanometer. One scale reading would correspond to the sound transmission of each portion of the chest.

It is known that the electrical resistance of human tissue varies with its physical condition. An attempt is being made to determine whether there is any way in which this fact can be made useful in discovering and locating diseased conditions in the lungs.

DISCUSSION

Dr. Henry A. Christian, of Boston, said that at the meeting of the National Research Council an endeavor had been made to bring together a group of biologists interested in the physical side of their work and a group of physicists interested in the biologic side of their study, so that the fundamental qualities of biologic material, which in the last analysis were probably physical, could be studied from this combined point of view. Hitherto there had been a great gap between these two branches. The working committee consisted of Dr. Williams, of New York; Professor Ives and Dr. Bovie, of Boston, and Professor Lilly, of Clark University.

Dr. Francis H. Williams, of Boston, asked if when the amplifier was used there was any difficulty from external noises, as, for instance, from the passing of street cars or automobiles. He wondered if with the use of the filters spoken of it would be possible to exclude undesirable noises.

Dr. L. O. Grondahl, of Pittsburgh (closing), said that as soon as one began to use the amplifier one's troubles increased. So far, in regard to external noises, exclusive of the noises in the stethoscope, there had been no difficulty. The motors if placed too near the instrument had been a disturbing factor, but these were easily placed at a convenient distance.

THE EFFECT ON BLOOD-PRESSURE AND THE NON-PROTEIN NITROGEN IN THE BLOOD OF EXCESSIVE FLUID INTAKE

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AND

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The nitrogen excretion in nephritis is generally thought to bear a certain relationship to the quantity of urine excreted. Bamberger taught that flushing out the kidney increased the urea elimination. Mohr[1] in von Noorden's clinic later, concluded that reduction of fluid to the point where the daily output of urine fell below 1200 c.c. often lead to urea retention. On the other hand the maximum nitrogen elimination was obtained with a daily excretion of 1500 c.c. of urine. Von Noorden strongly urged that excessive quantities of fluid be avoided on account of the danger of raising the blood-pressure. He advised that the fluids be restricted sufficiently to maintain a daily output of 1500 c.c. of urine and as a safeguard once a week a flushing out day where the fluid intake is increased to the point where the primary output reaches two to three liters.

This teaching of von Noorden has been quite widely accepted although many have questioned whether the apprehension regarding the danger of raising the blood-pressure by increased fluids was well grounded. This is due to the physiological experiment that in the laboratory animals an intravenous injection of salt solution equivalent to 50 per cent. of the blood volume produced only a slight increase in the blood-pressure. With properly functioning kidneys this probably holds true in man.

[1] Beiträge zur Diatetik der Nierenkrankheiten, Ztschr. f. klin. Med., 1903, l, 377.

Recently, Foster and Davis[1] have studied 22 cases of nephritis determining the effect of water drinking on urea excretion. As a result of these observations they concluded, subject to individual variations, that when the daily output of urine was reduced below 1000 c.c. nitrogen retention resulted. The amount of urea excreted increased with the fluid taken and when the urinary excretion reached 2000 c.c. daily the nitrogen output exceeded the intake.

Minkowski[2] in reviewing the effect of water drinking in gout found considerable difference of opinion regarding its value in the elimination of uric acid. He considered that the maximum benefit is derived when $1\frac{1}{2}$ to 2 liters are taken in the twenty-four hours.

It was thought that it might be of interest to determine whether by increasing the fluid intake to a very high point by use of the Rehfuss tube the nitrogen elimination could be increased as shown by the reduction in the non-protein nitrogen in the blood. At the same time the effect on blood-pressure of high fluid intake could be observed. The observations were carried out on three patients. Two were cases of hypertension. One had only a very slight increase; the other a very decided increase in the non-protein blood nitrogen. Both had nocturnal polyuria and at no time had shown evidence of edema, although both came to the hospital on account of dyspnea on exertion. Apparently they both eliminated water well through the kidney. The urine contained an inconstant trace of albumin, and an occasional hyalin and granular cast. The third case was a typical, chronic gout of ten years' duration. The fingers showed to a very high degree the characteristic deformities. There were urate deposits in the ear cartilages and a large collection of urates in the olecranon bursæ. He no longer had any typical acute exacerbation, but rather prolonged periods of increased discomfort followed by weeks of comparative ease. The blood-pressure was only moderately elevated, 165 systolic. The urine did not contain any albumin or casts.

During the period of observation all these patients were on the hospital nephritic diet which includes all the carbohydrate foods.

[1] The Effect of Water Intake on Nitrogen Retention in Nephritis, Am. Jour. Med. Sc., 1916, cli, 49.

[2] Gicht, 1903.

In the portions ordinarily served this diet contains between 50 and 60 grams of protein.

The non-protein nitrogen of the blood was determined twice at intervals of four or five days preceding the water drinking test. The mean of these two readings was taken as the average. The water was introduced through the Rehfuss tube, the patient being given $2\frac{1}{2}$ liters every three hours from 9 A.M. to 6 P.M. or a total of 10 liters daily. This was continued for six days and twenty-four hours after completing the test the non-protein blood nitrogen was again determined. The time consumed in taking any one portion of fluid, *i. e.*, $2\frac{1}{2}$ liters, varied from fifteen to twenty-five minutes.

The retention of the water was determined chiefly by repeatedly weighing the patient. The urinary output for the various periods was also recorded.

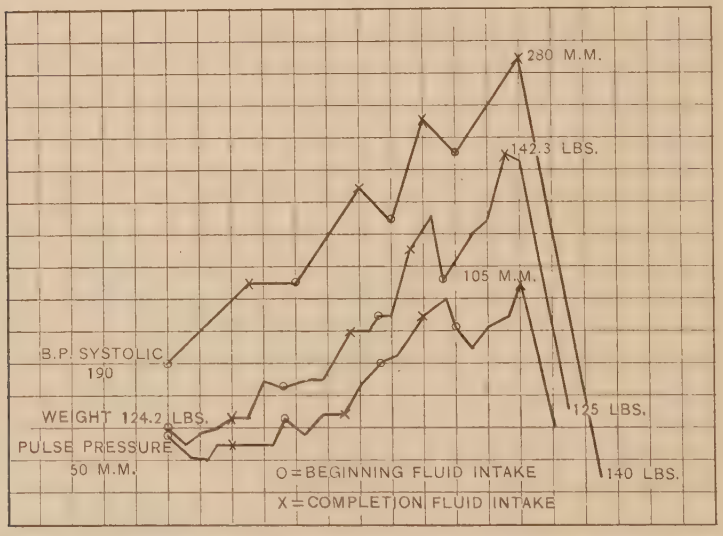

CHART I.—Showing changes in blood-pressure and weight with each successive fluid intake and the level twelve hours later.

I. K., aged thirty-five years, had been in the county hospital repeatedly during the past three years. His chief complaint had been dyspnea on exertion, which rapidly subsided with a moderate degree of physical quiet. His systolic blood-pressure was usually above 200. The maximum reported was 250. There was no evidence of edema. The urine contained an inconstant trace of albumin and an occasional granular or hyaline cast. His

phthalein output in three hours was 80 per cent. His urea nitrogen was 24.28 mg. per 100 c.c. of blood. The total non-protein nitrogen was 40.83 mg. The following protocol gives the record for one twenty-four-hour period:

PROTOCOL I.

	Time.	Systolic.	Diastolic.	Pulse pressure.	Weight, pounds.	Urinary output.
Dec. 20, 1919						
First 2½ liters:						
Before taking.	9.00 A.M.	160	108	52	124.2	
¼ taken . .	9.15 A.M.	150	100	50	....	9 to 12 A.M., 850
½ taken . .	9.27 A.M.	155	110	45		c.c. clear urine
¾ taken . .	9.35 A.M.	158	110	48		voided.
At completion	9.42 A.M.	162	115	47	129.2	
½ hour later .	10.15 A.M.	162	115	47		
1 hour later .	10.40 A.M.	180	120	60		
Second 2½ liters:						
Before taking.	12.00 P.M.	175	120	55	128.6	From noon till 3
¼ taken . .	12.10 P.M.	180	123	57		P.M.
½ taken . .	12.17 P.M.	180	123	57	....	1400 c.c. clear,
¾ taken . .	12.22 P.M.	188	130	58		pale urine
At completion	12.40 P.M.	205	145	60	134.0	voided.
1 hour later .	1.30 P.M.	205	132	73		
Third 2½ liters:						
Before taking.	3.10 P.M.	210	115	95	132.2	From 3 to 6 P.M.,
¼ taken . .	3.20 P.M.	210	125	85		1575 c.c. of
¾ taken . .	3.43 P.M.	230	140	90		urine voided.
At completion	3.50 P.M.	242	142	100	137.5	
1 hour later .	4.40 P.M.	255	150	105		
Fourth 2½ liters:						
Before taking.	6.00 P.M.	225	130	95	136.3	
¼ taken . .	6.10 P.M.	230	140	90	....	From 6 to 9 P.M.
½ taken . .	6.17 P.M.	240	145	95		of the next day,
¾ taken . .	6.25 P.M.	255	155	100		8600 c.c. of
At completion	6.35 P.M.	287	180	107	142.3	urine voided.
1½ hours later	8.00 P.M.	280	180	100		
Dec. 21, 1919.	9.00 A.M.	140	90	..	125.8	

Patient had no bowel movement during the time these data were being taken. At the end of the third five liters he complained of headaches and dizziness, which continued throughout the night. Claims he did not sleep during the entire night because of headaches, dizziness and general depression, with frequent urination. Meals were taken at 11 A.M., 5 P.M. and 8 A.M.

Summarizing the results in this table the systolic and diastolic pressure rose steadily, with the exception of temporary remissions between fluid intake periods from the beginning to the end of the test. The systolic

pressure increased from 160 to 287, the diastolic from 108 to 180 and the pulse-pressure from 55 to 107. His increase in weight from the beginning to the end of the experiment was 18.1 per pound. The following morning the weight had fallen to within 1.6 pounds of that preceding the experiment. He first began complaining of headache and dizziness about one hour after completing the second 2½ liters, which corresponds closely to the increase in pulse-pressure. During the other five days of the test he invariably complained of headache at this same period. At no time was there any visible subcutaneous edema. That the volume of the blood was probably definitely increased is shown by the pulse-pressure. The urea nitrogen twenty-four hours after this six-day period of water drinking was 25.5 mg., the total non-protein nitrogen 37.2 mg. as compared with 24.28 and 40.83 mg. before the test. The uric acid was 3.08 before and 1.51 after. The creatinin was 1.56 mg. before and 1.48 mg. after the test. The urea nitrogen actually increased slightly while there was a small reduction in the total nitrogen. These changes, however, may be considered negligible, as they represent only the normal variations. The reduction in the uric acid would appear to have been the result of the treatment, as a week after it was discontinued the uric acid had increased to 2.05. During the week following the patient was given the same amount of water during one night in order to see if the retention of fluids would be the same as during the day.

The maximum systolic pressure was somewhat less during the night than during the day experiment (260 as compared with 280). That the water was eliminated much more readily at night is shown by the gain in weight which was only 8.9 pounds.

The second patient tested was clinically similar to No. 1, with the exception that the non-protein nitrogen was high. The systolic blood-pressure ranged around 200. The urine contained a trace of albumin and an occasional hyaline and granular cast. The urea nitrogen was 56 mg.; the total nitrogen, 72.9 mg.; uric acid, 6.59 mg.; creatinin, 3.3. On account of the marked distress following 5 liters of fluid the patient was given 7500 c.c. daily the first two days and 5 liters daily the remaining four days.

Immediately after this he felt restless and dizzy and complained of a feeling of fulness in the abdomen, but did not seem worse than after the other two doses. However about one hour later he had a severe chill with nausea, vomiting, dyspnea, headache and cramps in his legs. This lasted all night, but by morning he was all right. Urine, 2100 c.c.; sp. gr., 1004.

In this patient the systolic blood-pressure rose from 200 to 242; the diastolic from 104 to 140. The pulse-pressure showed extreme variation, reaching its maximum of 122 at the end of the test. The increase of weight was 9¼ pounds. This patient complained of dizziness following the administration of each portion, and one hour after the third portion had a chill with vomiting and cramps in the leg. For this reason no attempt

was made to increase the fluid beyond 7500 c.c. The day following the same symptoms followed the third portion and in the few following days only 5000 c.c. was given daily. The urea nitrogen before the test was 56 mg.; the non-protein nitrogen, 72.9 mg.; uric acid, 6.6 mg.; creatinin, 3.3 mg. Twenty-four hours after completion of the six days' test the urea nitrogen was 54.1 mg.; the non-protein nitrogen, 69.6 mg.; uric acid, 5.9 mg.; creatinin, 2.45 mg. The slight reduction in the urea nitrogen and total nitrogen is probably negligible as variations of this degree occur normally.

PROTOCOL II.

Water was given during the night of December 26 and 27, 2½ liters at three-hour intervals as usual, with the following results:

	Time.	Systolic.	Diastolic.	Pulse pressure.	Weight, pounds.	Urinary output.
First 2½ liters:						
Beginning .	6.00 P.M.	170	100	70	131.7	6 to 9 P.M., 1180
¼ taken . .	6.05 P.M.	175	105	70		c.c. pale urine
¾ taken . .	6.13 P.M.	185	115	70		voided.
At completion	6.25 P.M.	210	120	90	137.2	
2 hours later .	8.00 P.M.	185	115	70		
Second 2½ liters:						
Beginning .	9.05 P.M.	190	110	80	134.2	From 9 until
⅓ taken . .	9.11 P.M.	195	115	80		midnight, 1800
⅔ taken . .	9.15 P.M.	210	120	90		c.c. of urine
At completion	9.27 P.M.	220	120	100	139.0	voided.
Third 2½ liters:						
Beginning .	12.07 A.M.	180	100	80	134.0	From midnight
⅓ taken . .	12.13 A.M.	205	115	90		until 3 A.M.,
⅔ taken . .	12.30 A.M.	220	120	100		1950 c.c. urine
All taken . .	12.30 A.M.	230	130	100	138.9	was voided.
Fourth 2½ liters:						
Beginning .	3.05 A.M.	225	130	95	135.5	3 to 6 A.M., 2760
½ taken . .	3.15 A.M.	225	130	95		c.c. voided.
¾ taken . .	3.19 A.M.	230	130	100	....	6 to 9 A.M., 1900
At completion	3.25 A.M.	260	155	105	140.6	c.c. voided.
At	9.00 A.M.	180	105			
Later . . .	12.00 A.M.	160	100	..	.....	Noon till 3 P.M., 1330 c.c. voided.
Later . . .	3.00 P.M.	140	90	..	133.0	1140 c.c. voided.
Dec. 28, 1919.	11.00 A.M.	155	90			

The third patient was a high-grade chronic gout of ten years' duration. His phthalein output was 12 per cent. in three hours. Systolic blood-pressure ranged from 150 to 170.

This patient took 10 liters of water daily for six days without inconvenience. He eliminated the fluid almost as rapidly as it was taken. The

maximum increase in blood-pressure was 15 mm. and he did not show any appreciable gain in weight.

The urea nitrogen before the test was 66 mg.; after the test 69.4 mg. Total non-protein nitrogen before the test, 92 mg.; after the test, 97 mg. Uric acid before, 8.25 mg.; after, 4.85 mg.

PROTOCOL III.

	Time.	Systolic.	Diastolic.	Pulse pressure	Weight.
Dec. 2, 1920.					
First 2500 c.c. of tap water:					
Beginning	9.20 A.M.	200	104	96	137.75
¼ taken	9.25 A.M.	198	115	83	
¾ taken	9.36 A.M.	206	96	110	
All taken	9.40 A.M.	204	122	82	142.25
2 hours later . . .	11.30 A.M.	206	110	96	

Patient felt a little dizzy immediately, but it wore off soon. Before the next dose he passed 600 c.c. of urine; sp. gr., 1008 and had a bowel movement.

Second 2500 c.c. of tap water:					
Beginning	12.52 P.M.	208	120	88	142.00
¼ taken	1.00 P.M.	208	110	98	
¾ taken	1.10 P.M.	212	125	87	
All taken	1.16 P.M.	206	140	66	146.00
2 hours later . . .	3.10 P.M.	198	120	78	

Patient was a little restless and dizzy immediately, but no worse than after the first dose. Before the third dose he passed 1200 c.c. of urine of 1006 sp. gr.

Third 2500 c.c. of tap water:					
Beginning	5.00 P.M.	210	125	85	142.50
¼ taken	5.03 P.M.	210	132	78	
¾ taken	5.10 P.M.	220	135	85	
All taken	5.15 P.M.	230	140	80	146.00
2 hours later . . .	7.00 P.M.	242	120	122	

This shows a very definite reduction in the uric acid, but an increase in the urea nitrogen and total nitrogen. It is highly probable that this reduction in the uric acid was the result of the treatment as repeated determination of uric acid previous to and following the test had never fallen below 6.25 mg. per 100 c.c. of blood. One week after the test the uric acid had increased to 9.17 mg. This is in accord with what occurred in Case I where there was a very definite decrease in the uric acid, but without change in the urea nitrogen. The patient with gout, however, in a later test where he was given 10 liters of water daily for eight days, showed a

slight increase in the uric acid in the blood from 6.17 to 7.25 mg. per 100 c.c. Atophan, 3 gms. daily for one week, did not reduce the amount of uric acid in the blood.

We wish to acknowledge the valuable assistance rendered by the interns on the service at Cook County Hospital.

SUMMARY. In patients with hypertension and presumably chronic interstitial nephritis, large amounts of fluid may cause a very decided increase in blood-pressure. Whether this rise occurs depends upon the promptness with which the kidneys function in excreting water.

In the three cases studied the taking of large amounts of fluid daily for a period of six days was without effect on the urea nitrogen in the blood. As it was not feasible to determine the nitrogen eliminated in the urine during this period, these results do not exclude the possibility of increased nitrogen output.

In two of these three cases the uric acid in the blood was definitely lessened. This was probably due to the treatment as following its discontinuance there was an increase to the previous level.

DISCUSSION

Dr. Harlow Brooks, of New York, asked if that was distilled water or ordinary tap water.

Dr. L. G. Rowntree, of Rochester, Minn., asked if the doctor made any studies of nitrogen excretion. He would particularly like to know about the uric acid disturbance. Did any of the patients develop edema?

Dr. Austin, of New York, said that in normal persons the urea excretion was increased by increasing water at the rate of 3 to 5 liters a day, but beyond that point increasing the urinary output did not increase the urea. Another point was that in bringing about excessive dysuria, taking of distilled water in large quantities was followed by a lag in dysuria, but taking of saline solution was followed by output of the amount of fluid ingested.

Dr. F. M. Allen, of New York, said that in regard to drinking of a large amount of water there were types of cases in which the tension would go up with drinking large amounts. These were the normal tension cases. In the hypertension cases, in which the water was eliminated rapidly, the

tension did not go up. If one gave these patients salt the tension would go up, and if a patient with a pressure of 200 got salt, then there would be fireworks. In one type of normal pressure there was a tremendous lag of excretion and the blood would show a volumentric increase, but there was no rise of pressure because the patient got edema. The blood showed great reduction in soluble substances and nitrogenous constituents. When excretion is increased the distilled water sweeps out some of the chloride and there is a fall in blood-pressure.

Dr. E. P. Joslin, of Boston, said that in considering the elimination of nitrogen one should bear in mind the total metabolism of the individual. In the usual quantity of liquid drunk the metabolism was little changed; with a large quantity metabolism was affected. Unless one remembered this metabolic change one might not account correctly for the nitrogen excretion.

Dr. Loevenhart, of Madison, Wis., asked if the rise in pulse-pressure was due to rise in pulse-rate. Was there an increase of cardiac output per beat?

Dr. H. A. Christian, of Boston, asked if there was a diuretic or non-diuretic effect.

Dr. H. O. Mosenthal, of New York, said that in considering this problem one conclusion would not apply to all cases for the reason that a diuretic effect produced by water would vary very greatly. Water ingested in large quantities instead of giving diureses might give oliguria; at times it might produce diminished water content of the body. The effects on blood-pressure might be interpreted from two different points of view: (1) A definite nervous effect on the individual; and (2) the tension of the nervous system might produce rise in blood-pressure.

Dr. Joseph L. Miller, of Chicago (closing), said that none of the patients showed any edema. There was a definite diuresis. One patient passed 3700 c.c. between 9 P.M. and 7 A.M.

ACUTE PSYCHOSES ARISING DURING THE COURSE OF HEART DISEASE

By DAVID RIESMAN, M.D.
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ACUTE mental disturbances sometimes appear during the course of heart disease with such startling suddenness as to disconcert the attending physician and to prove a severe shock to the patient's family. The majority of text-books are silent on this subject, yet the condition is one upon which both from the point of view of etiology and of prognosis much light is needed. Dr. Head, in 1901, in a masterly article,[1] called attention to the mental changes accompanying visceral disease, including heart affections; he concerned himself, however, chiefly with hallucinations of sight, sound and smell, and states of mild depression or exaltation, which he analyzed with very keen insight. In keeping with the opinion of the day in which he wrote, he speaks of aortic valve disease, mitral regurgitation and mitral stenosis, but does not mention that great group of cardiac affections in which valvular lesions play a subordinate or negligible part.

It is of course well known that cardiac patients often are depressed and irritable, particularly after decompensation has been established, and sleep, digestion and respiration are in consequence disturbed. The particular state of mind is closely related to the patient's temperamental make-up and to his philosophy of life. I once had under my care a woman, aged about forty years, with the most hopeless cardiac break, with dropsy, serous effusions, large liver, cyanosis, insomnia and orthopnea, who until her death maintained a perfect sweetness of disposition and a hopefulness of spirit

[1] Brain, 1901, 24, 345.

that was greater than any spes phthisica that I have ever witnessed. On the other hand, I have seen patients who when decompensation was far advanced, by their fretfulness and their unreasonable demands, made life miserable for family, doctor and nurse. But while such a mental condition is abnormal it cannot be called a true psychosis. Nor shall I consider among the cardiac psychoses the delirium of acute and subacute septic endocarditis, since that is dependent more upon the infectious toxemia than upon the heart disease as such.

The manifestations of true psychoses are quite varied. Among the more important types are the following:

1. *Hallucinations* of sight and sound, more rarely of smell. These were found by Head[1] to be most frequent in aortic disease. The auditory hallucinations consist chiefly of rhythmic sounds like the tolling of bells or of knocking; the visual usually take the form of the face of a man or woman with dimly outlined body standing at the foot of the bed or stalking slowly across the room. The patients as a rule recognize the hallucinatory character of the sound or vision and are disinclined to speak of it until the physician has gained their confidence. Hirschfelder[2] states that a number of patients admitted having hallucinations after he had assured them that visual hallucinations were not uncommon in their disease and were merely to be regarded as troublesome but not as significant features. All who gave positive answers accurately described the visual hallucination as detailed above.

The hallucinations are to be looked upon as misinterpreted sensations caused either by anemia or by venous stasis of definite brain centers—those connected with sight or hearing—or by circulatory or trophic disturbances in the corresponding peripheral end-organs. They are usually of a transitory character and do not affect the prognosis in any definite manner.

2. The most common cardiac psychosis is a state of *confusion*, in some cases present only as the patient awakens from sleep or is about to go to sleep; in others it is a more or less constant symptom. The patient confuses his surroundings, is disorientated as to

[1] Loc. cit.
[2] Diseases of the Heart and Aorta, Philadelphia, 1918, p. 229.

time but may become rational when his attention is sufficiently aroused. This mild type of psychosis is common in myocardial cases with auricular fibrillation with or without decompensation. The less the natural sleep the greater the confusion.

3. In some cases, especially in elderly persons suffering with fibroid myocarditis, the mental state is one of *excitation with decided disorientation*. Such a type is illustrated by the following case:

Mrs. F. H. W., aged seventy years, with cardiac hypertrophy and hypertension, dyspnea on exertion and a little edema of the lower limbs, suddenly began to exhibit a state of mental confusion and excitation which was most marked when she awakened from sleep. She would stare excitedly about the room, talk incoherently and try to get out of bed. When engaged in conversation, she answered most questions pertaining to herself quite well, but to those dealing with the day's events or with familiar contemporary history, she gave confused and inappropriate answers. There was no evidence of motor weakness or paralysis; indeed, she seemed surprisingly strong. The urine contained a faint trace of albumin, no casts, no blood, but a very large quantity of urates; its specific gravity ranged from 1012 to 1022.

The prognosis in such cases is not good, death usually following within a few weeks after the onset of the psychosis. The patient may, however, clear up if the myocardial degeneration has not gone too far and if no complications ensue. In the case just mentioned a pneumonia supervened.

In some cases the state of excitement alternates with one of complete apathy and silence—the patient may sit up promptly when the doctor approaches and may stare directly at him, but answers no questions and does not betray by any sign that he understands what is said to him. Such taciturn myocardial patients have to be watched as they may suddenly become agitated, get out of bed, and make powerful muscular efforts that may end in collapse.

4. Perhaps the most interesting, certainly the most startling disturbance arising in diseases of the heart is *acute mania* which may appear with the suddenness of an apoplexy and for a time defy all efforts at control. I have seen it appear under two conditions: in

acute pericarditis and in advanced decompensation of myocardial origin. Its occurrence in pericarditis was pointed out long ago by Da Costa. The late F. A. Packard was the first to bring it to my attention when I was his intern in the Philadelphia General Hospital. We had in our ward a woman, Louisa Wilbur, who had an acute fibrinous pericarditis, the cause of which I do not remember. One day without warning she suddenly became wild and maniacal and had to be restrained. She remained in her state of mania until death. This experience impressed upon me the importance of examining for pericarditis all cases of sudden wild delirium or mania.

Mania in the course of myocardial disease is illustrated by the following case: W. M. R., a physician, aged about fifty years, was brought to my office in June, 1914, in a state of extreme shortness of breath and collapse, which had come on while he was cranking a refractory motor car. Examination showed total arhythmia, an enlarged heart, enlarged liver but no edema of the extremities. Under rest and digitalis the patient improved; the auricular fibrillation, however, was very slow in subsiding. Although he never regained his full strength, he was able to do a little practice until the spring of 1915; then, despite treatment, he began to lose compensation rapidly. At the beginning of June he suddenly started one day to "act like a crazy man," as his wife expressed it. For six consecutive hours he raced around his library table, throwing his hands wildly about and exclaiming: "I am a thief; no I am not. You are a thief; no you are not. I am a liar; no I am not. You are a liar; no you are not." These phrases he repeated over and over without stopping as fast as he could talk for six solid hours. It was only after Dr. H. MacVeigh Brown, with whom I was seeing him, had given three large hypodermic injections of morphin that the man quieted down. For nearly a week, however, he remained in a state of great physical agitation. He talked incessantly, mostly in a facetious vein, but without much coherence. Throughout that time he slept neither night nor day. It was a marvel to all of us how his heart stood the strain. Toward the end of this period another strange thing happened—the urine, which had been very scanty, became greatly augmented, the dropsy disappeared, and the man was able to lie down flat, which he had not done for a long

time. He never regained his mind completely and died in stupor six days after the termination of the maniacal episode.

5. *Delusional States.* When delusions occur they usually take a persecutory form and render the patient most unhappy. While mania and mental confusion are not confined to any particular type of heart disease, I have seen delusions of persecution so far only in connection with lesions of the aortic valve. One of the cases was that of a young baker in my wards at the Philadelphia General Hospital, who had aortic stenosis of rheumatic origin. He thought he was being poisoned with gas by enemies in his shop. Under rest the delusion disappeared in a short time.

6. During attacks of Cheyne-Stokes breathing—a common symptom in cardiac disease—there is at times in the dyspneic period a state of mental excitement or delirium which subsides during the apneic period. The seizures of Adams-Stokes disease, which so closely resemble petit-mal, should also be mentioned here.

In considering *the causes of the cardiogenic psychoses* a number of possibilities suggest themselves:

1. The connection may be an accidental one. In an individual of psychopathic make-up the taint may at any time break forth quite independently of the existence of heart disease, although the latter would favor it by impairing the circulation. In asylums for the insane, cases in which the psychopathy is associated with disease of the heart are numerous. These chronic psychiatric cases do not, however, belong here, as this paper concerns itself only with acute manifestations.

2. A probable factor, in some cases at least, is disease of the kidneys, a frequent concomitant of disorders of the circulation. Uremia by itself is quite capable of producing psychoses, either of the maniacal or of the melancholic type. However, I do not believe that the passive congestion of the kidneys in decompensation of the heart, although often considered a true nephritis, is capable of producing a uremic state. As an accessory factor, it cannot be ignored.

3. I have sometimes thought that acidosis may play a part in the production of mental symptoms in cardiac disease. One often finds when the circulation is failing that the urine becomes intensely acid and throws down a heavy pinkish sediment of urates. This is such

a constant phenomenon that I look upon it as possessing diagnostic value. It occurs in secondary renal congestion; not in primary nephritis. A study of the subject of acidosis in diseases of the circulation—the blood carbon dioxide, the hydrogen ion concentration, the ketones and other acid bodies—may, in the future, yield valuable information.

4. That drugs and poisons may be a factor is a natural assumption. An amount of alcohol that in otherwise healthy persons might not do any recognizable harm, may in a patient with disordered circulation lead to a psychosis. Some older writers have held digitalis responsible for maniacal and other acute psychopathic outbreaks. Duroziez[1] reported a number of cases of delirium and coma, which he attributed to digitalis medication. H. O. Hall[2] also called attention to delirium and hallucinations during the course of the administration of digitalis. In one case cited by him (p. 490), it would certainly seem as if digitalis had been responsible for a condition of mental depression bordering on melancholia. Babcock (quoted by Hall) noted in two patients a peculiar mental and emotional state that disappeared after the use of digitalis was discontinued. In the one case, that of a woman, with mitral stenosis, the mental disturbance took the form of a sullen moroseness with taciturnity; while the other patient, a man with aortic insufficiency, manifested a mild delirium of a harmless kind.

At the present moment I have under observation a woman with auricular fibrillation, who, after about the third or fourth day, became confused and talkative. She did not seem to know where she was, although on the occasion of my visits she would answer questions rationally. She herself said, both to the nurse and to me, that she thought the dark medicine did not agree with her. The dark medicine was tincture of digitalis, with a very small amount of tincture of belladonna. I thought that she might have a prejudice, so I substituted digipuratum for the tincture of digitalis. But she also objects to that, and I am strongly inclined to stop the administration of digitalis altogether.[3]

[1] Gaz. hebdom., 1874, xi, 780.
[2] Am. Med., 1901, i, 598; Ibid., 1905, ix, p. 489.
[3] This was done but the psychosis continued, so that it is not likely that digitalis had anything to do with it.

While digitalis may in rare instances exert a direct action upon the brain, it is possible that in some cases when overdoses are given, it may, by disturbing the cardiac rhythm through its action on the conducting mechanism, still further impair an already inadequate circulation. On the whole, however, considering the universal use of the drug and the carelessness in dosage, one would expect that if digitalis could cause psychoses they would be much more frequent.

5. Several years ago I had the following experience: Mr. H. B. B., a man in the late fifties, was suffering with cardiovascular disease, with extreme dropsy. I tried digitalis and all other well-known diuretics without result. About that time agurin appeared on the market. I prescribed it and was amazed to find the urine output increased to an enormous degree, with a coincident rapid disappearance of serous effusions and of every trace of dropsy. During the time that the patient was putting out huge quantities of urine (in one day more than 200 ounces), he developed a delirious, incoherent state, which lasted several days and proved most distressing to his devoted family. I attributed it to a swamping of the system with the toxic material that had been held in solution in the dropsical fluid, and which, in order to reach the kidneys, had to return to the general circulation.

6. In cases in which the foregoing factors are lacking, in which the cardiac patient without neuropathic taint, nephritis, acidosis or exogenous intoxication, develops an acute psychosis, we may assume that it is due to some direct disturbance of the cerebral circulation, affecting the higher centers. At times there is probably syphilitic disease of the vessels, but that is not a prerequisite. Dana's hypothesis[1] concerning the part played by the neuronic synapses may help us to understand why, in disturbances of the circulation, alterations may occur in the psyche. Nevertheless, it is still a far cry from hypofunction of the synapses to an understanding of mental exaltation or depression, of hallucinations or of confusional states.

Not much need be said about treatment, which will vary with the type of disturbance found. Maniacal patients often do not

[1] Jour. Am. Med. Assn., April 24, 1920.

respond to morphin or any of its congeners. I have obtained better results with chloral, which I believe to be not so depressive to the heart as it is usually considered.

As regards diagnosis, it is always necessary to bear in mind that acute mania or melancholia may be symptomatic of visceral disease, in particular, of disease of the heart, and that patients so affected are not of necessity subjects for the asylum. The prognosis is governed by the state of the circulation—if the patient's heart holds out his psychosis will disappear.

DISCUSSION

Dr. George Blumer, New Haven, said that many of these cases were of syphilitic origin, especially those disturbances accompanying aortic lesions.

Dr. J. B. Herrick, of Chicago, said these disturbances developed largely as a result of the circulatory inhibition in the brain, and there was often very distinct evidence of toxemia. The disturbance of metabolism resulted in an accumulation of toxic material in the blood. Occasionally toxic material was introduced, for example, alcohol or digitalis, or occasionally bromides. Morphin, hyocine and bromine were often given with too free a hand. One other fact had been noted, the hopefulness of some cardiac patients; some, it was true, were irritable and nervous, but in some cases their hopefulness was comparable to that seen in acute phthisis. Dr. Blumer's point was well taken; aortic disease was often syphilitic, but it did not often have mental symptoms.

THE METABOLISM OF DIABETES

By ELLIOTT P. JOSLIN, M.D.
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To us physicians it would be a comfort if the metabolism of an individual could be adequately expressed in such simple terms as per kilogram body weight or per square meter body surface. It is true that these two factors are combined in the Du Bois height-weight formula, but even this demands two modifications to secure accuracy, namely, a correction for sex, since the metabolism of women is about 6 per cent. less than that for men for corresponding height and weight and second for age, because the total daily requirements of the body decrease approximately 7 calories each year. For this reason Du Boid applies corrections to his formula which makes it sufficiently accurate for clinical purposes. Harris and Benedict, however, have constructed a series of tables, based on actual metabolic measurements of over 239 men and women, in which height, weight, age, and sex are considered, and from these the metabolism of any individual can be predicted. It shows progress in calorimetric research that the normal basal metabolism as estimated by the two methods is but a few per cent. apart.

The total metabolism in diabetes is a varying factor. If one constructs an arbitrary base line—term it for convenience a normal line—it has been found in the studies at the Carnegie Laboratory based upon 449 experiments of two to four periods each with 111 diabetics, that the sum of the extreme variations above and below this line amount to 88 per cent., and that if an average is taken of all experiments conducted before June, 1914, when I first used fasting treatment, and of all since that date, the variations above and below the above assumed normal line are 27 per cent. For

this 27 per cent. variation in metabolism Dr. Allen must accept the responsibility, and this he will doubtless be the more ready to do when he learns that the average duration of life of the diabetic today is about twice as great as in 1914. An enormous variation in the metabolism of diabetics has therefore been demonstrated, and this has been shown to be closely related to the cases having been studied before or after undernutrition was inaugurated.

Thus far, with design, any statement as to an increase or decrease of the metabolism of diabetics above or below normal has been avoided. It can now, however, be affirmed without fear of contradiction from any source, that the average metabolism of the diabetics studied in this country was increased prior to June, 1914, and correspondingly decreased since that date. As to how much above normal was the metabolism of the group of diabetics once reported by Benedict and me before this Society, opinion has differed because of lack of agreement of a normal base line. Benedict and I with our first series placed it 21 per cent. above normal and with our second and larger series 15 to 20 per cent. in excess. The average of this same group on the basis of the Harris-Benedict tables is 11 per cent. If the Du Bois height-weight formula is employed with its latest modifications and the Du Bois normal base line employed the metabolism would probably be found to be about 5 per cent. below the above figures. Since June, 1914, the metabolism of the 76 cases of diabetes studied has been found to be 12 per cent. below the Harris-Benedict standards.

A relation exists between the severity of the disease and the metabolism, but this relation is lost unless the date June, 1914, is introduced. Prior to that date the metabolism was higher the more severe the case, and subsequent to it the metabolism was lower the more severe the diabetes. To a large extent these facts are explained by the severer cases in each group being those which were most rigorously either over- or underfed.

There is also a relation between acidosis and the metabolism, for there is a general tendency if the metabolism is above normal for it to rise with increasing acidosis. This relation, on the other hand, does not hold for those cases in which the metabolism is decreased. It is possible that the extreme degree of undernutrition which was in

process of development obscured the effect of the acidosis. This would appear the more probable when the metabolism of 6 cases was studied in 12 experiments of varying degrees of acidosis, and these cases compared with 4 normal individuals of corresponding heights and weights in a period of forced undernutrition. Here a direct relation between the height of the metabolism and the intensity of the acidosis was observed.

The respiratory quotient is in close connection with the metabolism. The data show that the lower the respiratory quotient the higher the metabolism tends to rise. Many interesting observations were encountered in connection with the respiratory quotient which will later be reported in detail.

The effect of the administration of levulose has been studied in 50 experiments on diabetics. The average of these experiments showed an increase of 17 per cent. in the metabolism. The more levulose given per kilogram body weight the greater the increase in the metabolism. This is not very different from Carpenter's levulose experiments with normal individuals. He obtained an increase in metabolism of between 15 per cent. and 24 per cent. according as to whether the single maximum effect of levulose or the total additional heat produced is studied. The results with diabetics are all the more surprising, because with normals the maximum rise in the respiratory quotient averages 18 points, whereas with nearly half the diabetics there was no rise at all, and even with the remaining half the change was slight.

Observations upon the metabolism in relation to the blood-sugar, blood-fat and non-protein nitrogen were also made. A distinct relation between the pulse and the metabolism was usually found. Besides the 50 experiments with levulose there were some 100 other food experiments. These data are eventually to appear in a Carnegie publication which should be printed in 1921.

DISCUSSION

Dr. F. M. Allen, of New York, said that diabetes was a disorder in which the total metabolism was involved. Overfeeding the patient raised his metabolism. The patient must learn to accept his lowered metabolism, then he could live indefinitely. One must not try to drive his renal function.

THE INFLUENCE OF PROTEIN FOOD ON INCREASED BLOOD-PRESSURE[1]

By HERMAN O. MOSENTHAL, M.D.
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Protein food has generally been regarded as having a definite influence on blood-pressure. A diet high in proteins has been supposed to raise blood-pressure, and *vice versa*. This principle has been widely applied in all diseases associated with hypertension, and, as a rule, a diet low in proteins, especially in meats, has been prescribed for patients exhibiting an increased arterial pressure.

It is disappointing to note on what very meager evidence the above ideas are based. Goodall[2] published some very convincing observations which showed that a distinct drop in blood-pressure occurred in cases of chronic interstitial nephritis on a low protein diet. Practically all other efforts in this direction, and they are very numerous, have confined themselves to general statements which either expressed an approval, or, in some instances, a disbelief, in this relation of blood-pressure to diet; however, the concrete evidence of carefully observed cases has been largely lacking.

The following blood-pressure determinations were made on patients who had been in bed for several days. This allowed the arterial tension to assume the lower level which mental and physical relaxation bring about. The manometer readings were made at approximately the same time every day. The patients were kept in bed continuously during this study. The long period over

[1] The cases reported in this paper were observed at the Medical Clinic of the Johns Hopkins Hospital.

[2] Boston Med. and Surg. Jour., 1913, clxviii, 760.

which some of the observations were carried out serves as a control for the fluctuations that may occur in the level of blood-pressure of individuals suffering with hypertension. During the periods of low-protein feeding the diets did not contain meat, meat products (such as soups or gravies) or fish. These foods were taken in considerable amounts on the days of high protein feeding.

Cases 1, 2 and 3.—Neither a high nor a low protein diet have any remarkable effect upon the blood-pressure in a few days.

Table I.—Blood-pressure Observations on Case 1. (Chronic diffuse nephritis of slight degree.)

Day.	Blood-pressure.		Blood, mg. per 100 c.c.	Diet.	
	Systolic.	Diastolic.	Total N. P. N.	Protein, gm.	Character.
1	164	110	31.8	20	Low protein.
2	165	108	....	19	
3	162	106	....	20	
4	152	110	29.7	21	
5	156	96	....	166	High protein.
6	160	96	....	196	
7	175	110	....	201	
8	170	106	....	136	
9	150	106	37.0	150	

Table II.—Blood-pressure Observations on Case 2. (Female, aged fifty-six years, arteriosclerotic kidney of moderate degree; the urine contains a trace of albumin and a few fine granular casts; the urinary specific gravity varies between 1005 and 1015; 45 per cent. of phenolsulphonephthalein is excreted in two hours and ten minutes.)

Day.	Blood-pressure.		Blood, mg. per 100 c.c.	Diet.	
	Systolic.	Diastolic.	Total N. P. N.	Protein, gm.	Character.
1	175	118	21.2	11	Low protein.
2	155	114	....	10	
3	170	122	....	12	
4	156	120	25.4	10	
5	155	100	....	114	High protein.
6	166	104	....	107	
7	154	100	....	119	
8	184	70	....	131	
9	160	115	33.9	123	

Table III.—Blood-pressure Observations on Case 3. (Male, aged sixty-three years, essential hypertension; renal function normal.)

Day.	Blood-pressure.		Diet.	
	Systolic.	Diastolic.	Total calories.	Protein, gm.
1	204	124	2061	126
2	205	120	2055	125
3	...	...	2056	124
4	185	120	2063	126
5	218	138	2063	126
6	189	117	2212	78
7	166	110	2060	125
8	205	125	2061	126

Case 4.—There is no notable change in the level of the arterial pressure on a high or a restricted protein intake, while the total number of calories is maintained at a constant level.

Table IV.—Blood-pressure Observations on Case 4. (Male, aged sixty-seven years. Secondary contracted kidney; at times a trace of albumin and a few hyalin and granular casts; a phthalein excretion of 25 per cent. in two hours and ten minutes; urea nitrogen, 34 mg. per 100 c.c. of blood; moderate arteriosclerosis.)

	Blood-pressure.		Diet.		
Day.	Systolic.	Diastolic.	Protein, gm.	Total calories.	Character.
1	190	120	91 (28)[1]	2344	Normal diet.
2	175	105	86 (19)	2498	
3	195	115	80 (28)	2501	
4	190	110	125 (69)	2065	High protein.
5	178	112	125 (74)	2065	
6	194	120	125 (75)	2065	
7	183	125	125 (76)	2065	
8	188	115	125 (76)	2065	
9	187	119	125 (69)	2065	
10	190	116	125 (79)	2065	
11	170	103	125 (64)	2065	
12	175	105	125 (80)	2065	
13	195	108	125 (78)	2065	
14	182	104	125 (68)	2065	
15	185	113	125 (76)	2065	
16	187	107	125 (80)	2065	
17	175	115	125 (72)	2065	
18	194	109	50 (18)	2065	Restricted protein.
19	181	109	50 (16)	2065	
20	178	100	50 (29)	2065	
21	173	103	50 (18)	2065	
22	209	114	50 (29)	2065	
23	178	105	50 (16)	2065	
24	203	115	50 (11)	2065	
25	188	117	50 (16)	2065	
26	173	106	50 (16)	2065	
27	183	110	50 (16)	2065	
28	182	110	50 (16)	2065	
29	182	110	50 (17)	2065	
30	190	115	50 (14)	2065	
31	206	125	50 (17)	2065	
32	190	125	50 (14)	2065	
33	210	120	50 (20)	2065	
34	195	115	50 (19)	2065	
35	201	115	50 (31)	2065	
36	185	115	50 (21)	2065	
37	205	110	50 (13)	2065	
38	205	105	50 (29)	2065	
39	202	112	50 (18)	2065	

Cases 5 and 6.—The low protein diet is effective in producing a diminution in the blood urea nitrogen, but the blood-pressure remains unchanged.

[1] Figures in parentheses are the quantity of protein from meat or fish.

TABLE V.—Blood-pressure Observations on Case 5. (Male, aged thirty-five years; secondary contracted kidney; albuminuria moderate; a few hyalin and fine granular casts; phthalein excretion, 21 per cent., in two hours and ten minutes; low fixed specific gravity of urine; albuminuric retinitis.)

Day.	Blood-pressure.		Blood, mg. per 100 c.c.		Diet.	
	Systolic.	Diastolic.	Urea N.	Total N. P. N.	Protein, gm.	Character.
1	210	140	61	97	..	Low protein.
2	...	...	..	..	15	
3	210	140	..	..	18	
4	...	...	41	70	20	
5	215	140	..	..	43	
6	...	...	..	..	53	100 gm. turkey added one day only.
7	210	135	..	..	28	
8	...	...	..	..	29	
9	...	...	..	..	25	
10	218	140	24	38	26	
11	...	...	..	..	25	
12	...	...	..	..	31	
13	210	145	..	..	44	
14	...	...	..	..	33	
15	220	145	..	..	29	
16	...	...	..	..	26	
17	210	140	..	..	24	
18	...	...	..	..	33	
19	213	145	15	22	28	
20	..	...	..	..	21	
21	200	139	..	32	65	Bread ± 300 gm. added.
22	...	...	..	..	54	"
23	...	...	..	..	53	"
24	224	145	21	32	66	"
25	...	...	..	..	68	"
26	238	148	..	..	29	"
27	213	140	..	..	59	"

TABLE VI.—Blood-pressure Observations on Case 6. (Male, aged thirty-two years; an advanced case of arteriosclerotic kidney; the urine contains a trace of albumin and a few granular casts; the specific gravity is absolutely fixed at a level of 1010; only a trace of phthalein is excreted in two hours and ten minutes; Ambard's constant is 0.77; the blood-urea nitrogen is given in the table.)

Day.	Blood-pressure.		Blood, mg. per 100 c.c.	Diet.		
	Systolic.	Diastolic.	Urea N.	Total calories.	Protein, gm.	Character.
1	191	122	105	850	17	Low protein.
2	196	124	...	1571	15	
3	182	116	...	1626	16	
4	180	120	...	1721	16	
5	185	123	...	1755	19	
6	194	119	...	1778	20	
7	200	125	...	1838	20	
8	212	125	...	1687	20	
9	192	115	66	2396	82	

CASE 7.—A diet low or restricted in proteins is not accompanied by a drop in blood-pressure. An increase of the caloric value of the food results in no changes in the arterial tension.

TABLE VII.—Blood-pressure Observations on Case 7. (Male, aged forty-six years; secondary contracted kidney, with considerable impairment of renal function; phthalein, 26 per cent., in two hours and ten minutes; blood-urea nitrogen, after low protein diet, 27 mg. in 100 c.c.; Ambard's constant, 0.144; albuminuria, about 1 gm. per liter; many hyalin and granular casts.)

	Blood-pressure.		Diet.						
						Additions to diet.			
Day.	Systolic.	Diastolic.	Total calories.	Protein, gm.	Character.	Eggs, No.	Oatmeal, gm.	Milk, cream, c.c.	Meat, gm.
1	230	160	..	..	Ward diet				
2	219	155							
3	215	160							
4	219	161	..	..	Low protein				
5	235	158							
6	232	160							
7	230	140							
8	230	150	1676	22					
9	234	160	1722	17					
10	232	155	1937	22					
11	232	153	2038	25					
12	221	138	2116	34					
13	229	155	2274	36					
14	234	144	2136	38					
15	242	145	2299	47	....	3			
16	220	137	2302	49	....	3			
17	215	140	2300	48	....	3			
18	217	142	2110	39	....	2			
19	235	155	1552	17	Calories				
20	242	154	1513	17	Lowered				
21	222	153	1604	20					
22	231	145	1644	19					
23	224	145	1841	20					
24	228	145	1570	19					
25	224	155	2037	28	Calories				
26	228	145	2496	36	Raised				
27	218	135	2410	38					
28	220	138	2509	47	....	..	400	245	
29	229	150	2641	48	....	..	400	290	
30	232	145	2601	48	....	..	400	320	
31	218	145	2781	51	....	..	400	260	
32	214	147	2504	50	....	..	400	260	
33	220	145	2619	50	....	..	400	290	
34	224	145	2616	50	....	..	400	230	
35	218	143	2492	47	....	..	400	260	
36	220	142	2511	59	....	..	400	230	50
37	220	145	2669	63	....	..	400	280	50
38	224	152	2767	63	....	..	400	180	50
39	224	138	2761	74	....	..	400	280	100
40	218	138	2772	77	....	..	400	230	100
41	225	135	2718	65	....	..	400	230	50
42	230	148	2873	70	....	..	400	130	50
43	228	144	3026	73	....	..	400	310	100
44	214	145	2719	74	....	..	400	230	100
45	...	...	2819	75	....	..	200	260	100
46	232	145	2361	75	....	..	200	335	125
47	230	142	2819	75	....	..	200	260	150

CASE 8.—There is a tendency for a diminution of the blood-pressure with a diet very low in protein and low in caloric value.

TABLE VIII.—Blood-pressure Observations on Case 8. (Female, aged forty-one years; secondary contracted kidney, with marked impairment of renal function; phthalein, 10 per cent. in two hours and ten minutes; blood-urea nitrogen, 45 mg. in 100 c.c.; specific gravity of the urine fixed at a level of 1010; marked albuminuria and many hyalin and granular casts.)

	Blood-pressure.		Diet.		
Day.	Systolic.	Diastolic.	Protein, gm.	Total calories.	Character.
1	188	108	10	489	Low protein.
2	...	...	14	972	
3	190	110	14	898	
4	190	109	10	888	
5	175	100	11	664	
6	165	80	9	713	
7	165	80	9	897	
8	160	85	6	583	
9	155	84	9	766	
10	163	90	8	688	
11	150	85	8	623	
12	160	85	8	538	
13	164	95	8	714	
14	...	...	8	561	
15	185	115	7	608	

CASE 9.—A distinct drop in the blood-pressure occurs with the initial period of low protein diet. The original height of the blood-pressure is promptly resumed when 250 gm. of meat are added to the diet. When the meat is discontinued and the low protein diet substituted the blood-pressure does not fall to the previous level which the first period of low protein feeding produced.

TABLE IX.—Blood-pressure Observations on Case 9. (Male, aged twenty-five years; secondary contracted kidney, with marked impairment of renal function; phthalein, 10 per cent. in two hours and ten minutes; blood-urea nitrogen as in the table; Ambard's constant, 0.63; albuminuria marked; hyaline and granular casts.)

	Blood-pressure.		Blood, mg. per 100 c.c.		Diet.	
Day.	Systolic.	Diastolic.	Urea N.	Total N. P. N.	Protein, gm.	Character.
1	165	120	..	...	..	"Ward, light."
2	165	120				
3	160	90				
4	166	100				
5	165	103				
6	160	100	99	125		
7	163	100	..	...	5	Low protein.
8	165	100	..	...	7	
9	160	105	..	...	4	
10	150	98	..	...	6	
11	146	97	..	...	8	
12	145	95	..	...	10	
13	125	88	126	145	9	
14	125	85	..	...	8	
15	125	90	..	...	10	

TABLE IX (Continued).

Day.	Blood-pressure.		Blood, mg. per 100 c.c.		Diet.	
	Systolic.	Diastolic.	Urea N.	Total N. P. N.	Protein, gm.	Character.
16	125	90	..	...	9	
17	130	80	..	...	11	
18	125	85	..	...	10	
19	125	85	..	...	9	
20	127	82	103	123	9	
21	130	85	..	...	11	
22	135	88	..	...	13	
23	135	88	..	...	15	
24	145	98	..	...	15	
25	145	103	..	...	12	
26	160	103	..	...	14	
27	165	112	..	...	13	
28	150	103	49	66	17	
29	140	95	..	...	10	
30	137	88	..	...	16	
31	135	90	..	...	12	
32	140	97	..	...	13	
33	143	98	..	...	15	
34	145	98	32	...	13	
35	147	100	..	...	68	250 gm. meat added
36	155	105	..	...	75	
37	169	122	..	...	52	
38	170	120	64	...	72	
39	170	120	..	...	73	
40	170	120	..	...	52	
41	170	120	..	...	52	
42	168	115	..	...	84	
43	169	118	..	...	47	
44	167	116	..	...	26	
45	150	105	63	95	53	
46	155	107	..	...	75	
47	163	107	..	...	74	
48	170	110	..	...	71	
49	170	117	..	...	16	Meat discontinued.
50	170	113	..	...	16	
51	168	110	..	...	14	
52	170	115	55	79	17	
53	165	112	..	...	10	
54	169	122	..	...	18	
55	172	117	..	...	17	
56	168	120	..	...	18	
57	168	120	..	...	16	
58	173	117	..	...	18	
59	170	115	30	41	17	
60	170	116	..	...	19	
61	180	120	..	...	20	
62	...	...	..	...	21	
63	...	...	..	...	16	
64	175	120	..	...	14	
65	182	116	23	32	14	
66	180	116	..	...	18	
67	182	120	26	36	24	

Conclusions.—From these observations it would appear that it is exceptional for a low protein diet to diminish the blood-pressure or a high protein diet to raise it. Case 9, however, shows that this may occur. This patient was extremely ill, as the great impairment of renal function indicates, and was necessarily maintained in a state of undernutrition, since any attempts to increase the food resulted in uremic symptoms. However, even in this case a second period of low protein feeding failed to bring the blood-pressure to the low level previously obtained.

The diminution of the waste products in the blood, as indicated by a lowering of the blood urea nitrogen, was without effect upon the blood-pressure. Changes in the caloric value of the diet, for a short time at least, did not influence the blood-pressure.

Discussion.—The basis upon which the impression that a low protein diet reduces blood-pressure rests may possibly be found in the recent report of F. G. Benedict[1] and his collaborators. These investigators demonstrated that by underfeeding the blood-pressure of healthy, young, male adults could be distinctly reduced. This change was accompanied by various other phenomena, among them a secondary anemia. These facts furnish a suggestion as to the therapeutic application of diet to hypertension. A subcaloric mixed diet may be continued for a considerable period, probably with beneficial effect. If the health and strength of the patient are to be maintained it is advisable to regulate the amount of the diet according to the hemoglobin content of the blood. The hemoglobin percentage should not fall below 85 per cent. From the data given in the present communication it is evident that in most instances a low protein diet continued for a period of a few weeks is without effect upon the blood-pressure of cases of hypertension.

[1] Human Vitality and Efficiency under Prolonged Restricted Diet, Carnegie Institution of Washington, Publication No. 280, 1919.

DISCUSSION

Dr. Joseph L. Miller, of Chicago, said that he had tried diets with 25 grams of protein for five or six weeks, then for an equal time, diet with high protein, and there was no effect noted on the blood-pressure.

Dr. S. Solis-Cohen, of Philadelphia, said that the question for the clinician was not purely one of high or low protein, but one of the character of the protein. He had the impression that there was a considerable difference in the protein of meat and that of milk.

Dr. Herman Mosenthal, New York (closing), said that for a great many years workers had noted a difference in the character of the proteins, and this was worth while considering. Intestinal putrefaction might have played a part in some of these cases, but as to the effect of the amount of protein absorbed, in some of these cases, on the system itself, he did not believe there was any difference in the effects of the proteins.

THE BLOOD-SUGAR TOLERANCE TEST AS AN AID IN THE DIAGNOSIS OF GASTRO-INTESTINAL CANCER.

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AND
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The great difficulty arising in the diagnosis of gastro-intestinal carcinoma, especially in the early stages, has long been recognized. In spite of our modern methods of investigation, including the most recent tests, the diagnosis in many instances remains obscure often until late in the progress of the disease and is frequently not revealed until exploratory incision establishes the true nature of the affection. Any additional help therefore which may lead to the solution of this difficult problem cannot but be of the greatest value. In the blood-sugar tolerance test we believe there has been added a further step in advance in this direction.

The fact that a high blood-sugar content is usually observed in patients affected with carcinoma has been known for many years. Freund,[1] in 1885, was the first to point out on the basis of seventy blood-sugar investigations that there is always a hyperglycemia in this disease; on the other hand he was unable to observe a similar condition in sarcomatous patients; he therefore recommends on this account that blood-sugar estimations be made as an aid in the differential diagnosis between the two affections.

Trinkler[2] investigated the blood-sugar content not only in carcinomatous patients but also in patients affected with other diseases, such as typhoid, pneumonia and tuberculosis. In these

[1] Allgemeine Wiener med. Zeitung, 1885, No. 9, S. 102.
[2] Centralblatt f. die medicinischen Wissenschaften, 1890, No. 28, S. 498.

observations there were 109 analyses, which were divided into two groups: (1) the estimation of sugar in the blood collected at operation, and (2) in that obtained at autopsy. A far greater hyperglycemia was observed in carcinoma than in other diseases.

The following table of Trinkler is interesting, as it presents the average, maximum and minimum percentage of sugar in the blood as observed by him in various diseases:

	Average.	Maximum.	Minimum.
Cancer	0.1819	0.3030	0.1023
Typhoid	.0950	.1022	.0875
Lobar pneumonia	.0943	.1092	.0813
Dysentery	.0838	.0915	.0796
Heart disease	.0737	.0897	.0664
Peritonitis	.0701	.0917	.0450
Tuberculosis	.0652	.0817	.0450
Syphilis	.0553	.0748	.0449
Nephritis	.0489	.0559	.0311
Uremia	.0375	.0559	.0311

Trinkler arrived at the following conclusions:

1. Hyperglycemia is always present in cancerous patients.

2. In carcinoma of the internal organs there is always a far greater hyperglycemia than in carcinoma of the skin or mucous membrane.

3. The cachexia of carcinomatous patients bears no relation whatever to the increase in blood-sugar.

In recent years many important investigations have been published by various observers regarding the significance of alimentary hyperglycemia as a test of sugar tolerance in health as well as in disease.

Jacobson[3] was the first to point out the importance of such investigations. He presents his results in 14 normal individuals following the administration of 100 gm. of glucose, and observes that an increase in blood-sugar occurs within 5 minutes after the administration of the glucose rising to its height in 30 minutes, which is followed by a gradual decline to the normal level in approximately 120 minutes, the blood-sugar increasing thus from 0.10 per cent. to 0.22 per cent. in 30 minutes and then gradually falling again to 0.12 per cent.

Hopkins,[4] working along similar lines, observed in his investigations that in health a moderate rise in blood-sugar (0.11 to 0.156

[3] Biochem. Ztschr., 1913, S. 411.

[4] Am. Jour. Med. Sc., 1915, cxlix, 254.

per cent.) occurs after the ingestion of 100 gm. of glucose reaching its height in from 30 to 120 minutes, and again quickly subsiding. He also notes that hyperglycemia is most pronounced in certain diseases, as in diabetes, pancreatic, nephritic and pituitary cases, in pneumonia, apoplexy, typhoid, tuberculosis and cancer.

A very elaborate and careful study of alimentary hyperglycemia has been published by Hamman and Hirschman.[5] These observers have pointed out that in normal individuals after the ingestion of 100 gm. of glucose the blood-sugar rises to a maximum concentration not exceeding 0.150 per cent., reaching its height in 30 minutes, which is followed by a gradual fall.

Similar observations were carried on in various diseases, *i. e.*, diabetes, nephritis, disturbances of the thyroid gland and hypophyseal functions, with rather definite results, and in some of these conditions rather typical curves were constructed, which are of considerable diagnostic significance.

The first careful investigations as to the glucose tolerance in cancer were published by Rohdenburg, Bernhard and Krehbiel.[6] Sugar determinations were made of the blood just before and again in 45 minutes, and 120 minutes after the ingestion of 100 gm. of glucose. While the normal individual presents an increase in the blood-sugar percentage, reaching its maximum in 45 minutes, which then gradually recedes to the normal, the cancerous patient begins with a normal blood-sugar, rising steadily in 45 minutes after the ingestion of the glucose to 0.18, or 0.2 per cent., and continues to rise or remain stationary for 120 minutes after the ingestion of the glucose, the percentage being either as high as the 45-minute reading or higher, reaching 0.28 per cent. or even to 0.35 per cent. The blood-sugar content then gradually begins to recede, approximating normal in from 180 to 240 minutes. This character of curve was observed in 24 cases of carcinoma and in 1 case of sarcoma, and was not found in other diseases.

According to these observers the sugar tolerance bears no relation to the location of the tumor, for primary carcinoma of the lung, sigmoid, stomach, heart and other organs all present similar findings.

[5] Arch. Int. Med., November, 1917, vol. xx.
[6] Jour. Am. Med. Assn., May 23, 1919, 1528.

Benedict and Lewis[7] report their observations in the blood-sugar content in 53 patients affected with malignant growths; the blood being taken 180 minutes after the ingestion of food. Of these cases 10, or 36 per cent., revealed a marked increase in blood-sugar, ranging from 0.12 to 0.16 per cent. At least 49 per cent. of the cases showed a tendency to hyperglycemia. According to these investigators there was noted a steady increase in the blood-sugar content as the disease progresses, reaching a maximum just prior to death, the hyperglycemia being in all probability a result of a constant demand of the growing tumor for carbohydrates.

Williams and Humphreys[8] observed a moderate increase in blood-sugar in 9 cases of carcinoma after the ingestion of an ordinary meal; they give no determinations following a dextrose meal; these investigations are therefore of but little clinical value. Cammidge[9] also calls attention to the hyperglycemia present in carcinoma, believing that in explanation of this finding there may be at hand a faulty functioning of the endocrine glands for a "similar hyperglycemic response followed by a delayed fall to normal has been observed in hyperthyroidism and exophthalmic goiter." Very recently, and since the completion of our study, Rohdenburg, Bernhard and Krehbiel[10] have published the results of an elaborate investigation on sugar mobilization based upon 228 cases. These authors call attention to three different types of reaction accompanying the sugar-tolerance test: In the first type, termed 1, the blood-sugar at the 45-minute interval rises above the zero hour figure and at the 120-minute interval is as high or higher than the 45-minute interval. In type 2 the rise in the 45-minute interval occurs as in type 1, but at the 120-minute interval the curve falls almost or completely to the original figure. In type 3 the initial sugar concentration is higher than or the same as that at 45 minutes, and the 120-minute interval shows a return to the original figure more or less complete, sometimes going even higher.

In nephritis 75 per cent. of the cases gave type 2 reaction; 60 per cent. of the tuberculous cases gave type 1 reaction; 72 per cent. of

[7] New York Med. Record, October 19, 1914, lxxxvi, 650.
[8] Arch. Int. Med., 1919, xxiii, 537.
[9] Practitioner, February, 1920.
[10] Am. Jour. Med. Sc., April, 1920.

the cases of syphilis showed type 2; 60 per cent. of the diabetic type 2 curve; 66 per cent. of the pregnancy cases gave type 1 reaction. These investigators have materially modified their previous views regarding the blood-sugar concentration in cancer. They found that 61 per cent. of gastric carcinomata and 50 per cent. of intestinal carcinomata gave type 1 reaction, and are of the opinion that the high sugar concentration observed in gastric carcinomata is in no way due to cachexia. They do not consider that any of the three types should be considered as diagnostic of any pathological condition, though generally conditions associated with increased cell growth present a greater percentage of type 1 reaction.

The great difficulties arising in the diagnosis of gastro-intestinal carcinomata, especially in the early stages, have led us to make a further study of the blood-sugar tolerance test as an aid in the differential diagnosis between carcinoma and other diseases of the abdominal organs, realizing full well, from the work of Rohdenburg and his co-workers, that a test of this character can serve only as an additional help in diagnosis, but must in no way be considered as specific of any disease.

In order to establish the practical utility of the blood-sugar tolerance test the method employed must be, though necessarily accurate, so simplified as to be easily carried out and not too time-consuming. In our examination we have followed the plan recommended by Hamman and Hirschman, as well as that of Rohdenburg, of giving after a night's fast 100 gm. of dextrose thoroughly dissolved in 300 c.c. of black coffee without additional sugar. The blood was withdrawn for examination by puncture from the arm vein just before and again in 45 minutes, and 120 minutes after the administration of the dextrose. The blood-sugar was determined by the Epstein method by employing a standardized apparatus which had been thoroughly tested as to its accuracy; we feel that by this method a simple as well as an accurate means is afforded for estimating blood-sugar. The advantages of this method are well known. It requires but 10 to 15 minutes to complete a determination of sugar, necessitating but a very small quantity of blood, and does not entail the employment of an expensive colorimeter, which thus renders the method especially useful for clinical work. Again,

the slight error common to our estimations can be of but minor significance, inasmuch as the test is a comparative one of at least three estimations conducted in each individual case, and in addition all of the determinations were made by the same individual under similar conditions. The urine was examined at varying periods in many instances, but sugar was but once observed in any of our cases up to 120 minutes after the ingestion of the glucose; occasionally it was present after 180 minutes.

In our investigations the blood-sugar tolerance was studied in 32 cases of carcinoma of the gastro-intestinal tract. All of the cases were typical of this disease; of these 17 were operated on and the diagnosis was thus confirmed, and in the remaining cases there were definite palpable abdominal masses in addition to the usual physical signs present in this affection; and the examination of the gastric contents as well as the roentgen ray and final outcome presented confirmatory evidence in every instance. Of these cases there were 19 of gastric carcinoma, of which there were 11 with obstruction at the pylorus, 1 at the cardia and 7 presented no obstructions; there were 9 cases of carcinoma of the stomach, with metastases in the liver and other abdominal organs; 2 of carcinoma of the rectum and of the cecum and 1 of the face and tongue. In addition, blood-sugar tolerance tests were made in 3 cases of uterine carcinoma; 1 case of breast cancer; 1 case of carcinoma of the prostate and spine; 1 case of uterine fibroid; 2 cases of sarcoma (1 of the jaw and 1 of the leg); in 8 cases of peptic ulcer; 2 cases of syphilis of the stomach; 3 cases of diarrhea and dysentery; 8 cases of achylia gastrica and chronic gastritis; 4 cases of cholelithiasis; 2 cases of chronic appendicitis; 11 cases of enteroptosis; 5 cases of nervous dyspepsia and 5 cases of intestinal stasis and mucous colitis, making 88 cases in addition to the 4 perfectly normal individuals studied for purposes of comparison. The sugar tolerance curves as observed in our cases may be classified into the following groups:

1. The Normal Curve. In normal individuals after the ingestion of 100 gm. of dextrose the blood-sugar content rises from 0.09 or even less to a height not usually above 0.165 per cent. within 45 minutes, falling usually more gradually within 120 minutes to about the level as that observed in the fasting state. This character of

curve was observed not only in normal individuals but also in the non-cancerous digestive disturbances other than those which have been classified in the following group. The two sarcoma cases also presented normal curves:

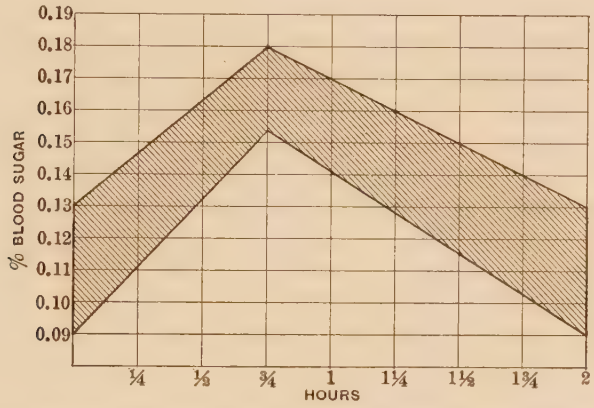

CHART I.—Maximum, minimum and average normal blood-sugar tolerance curve.

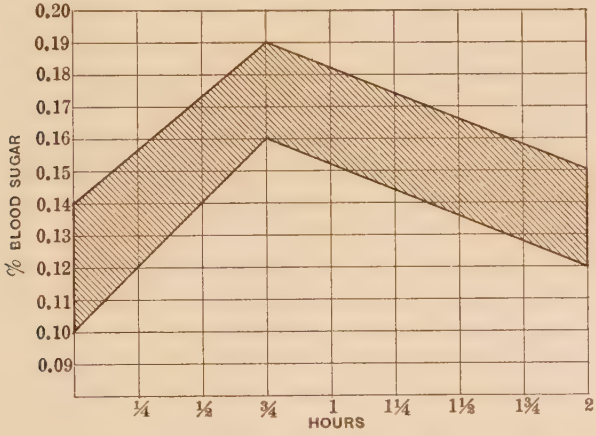

CHART II.—Maximum, minimum and average atypical normal curve.

2. THE ATYPICAL NORMAL CURVE. In certain individuals, often those affected with an achylia gastrica, an atypical normal curve is observed in which the blood-sugar content presents practically normal values in the fasting state, ascending to a height of from 0.16

to 0.18 per cent. within 45 minutes after the ingestion of the dextrose, falling slowly within 120 minutes to a level of from 0.13 to 0.15 per cent., but not any lower. This form of curve was found not only in our achylia cases but also in the cases of pyloric stenosis of benign origin.

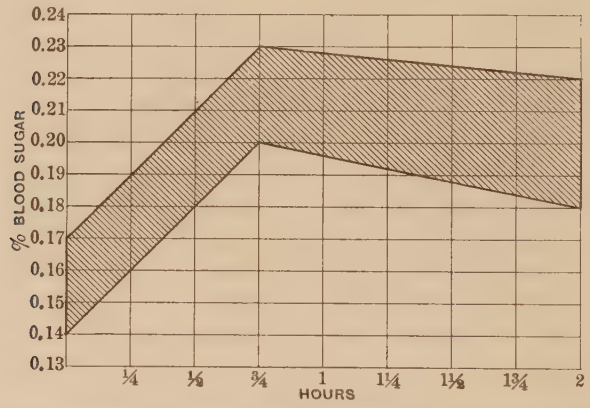

CHART III.—Maximum, minimum and average intermediate blood-sugar curve.

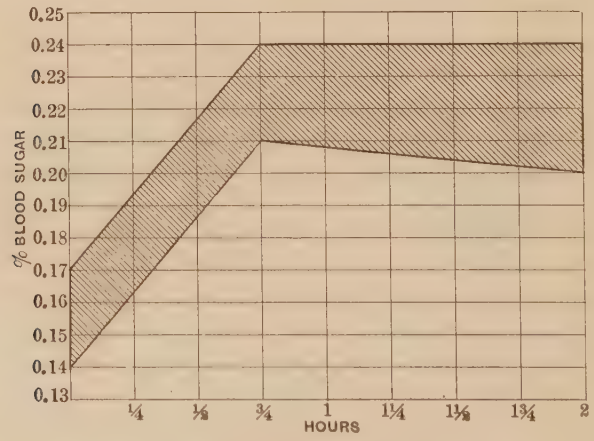

CHART IV.—Maximum, minimum and average blood-sugar tolerance curve in carcinoma of the gastro-intestinal tract.

3. THE INTERMEDIATE CURVE. The intermediate curve is usually observed in cases of carcinoma not associated with the gastro-intestinal tract, in which the blood-sugar content presents compara-

tively high values even in the fasting state of 0.14 to 0.17 per cent., and in which after the ingestion of 100 gm. of dextrose there is an initial rise to a height of from 0.2 to 0.23 per cent. within 45 minutes, followed within 120 minutes by a fall to a level of from 0.18 to 0.21 per cent., never descending at this time to the level observed in the fasting state. The intermediate curve was observed by us in 3 cases of uterine carcinoma, 1 case of carcinoma of the prostate and spine and 1 case of carcinoma of the breast.

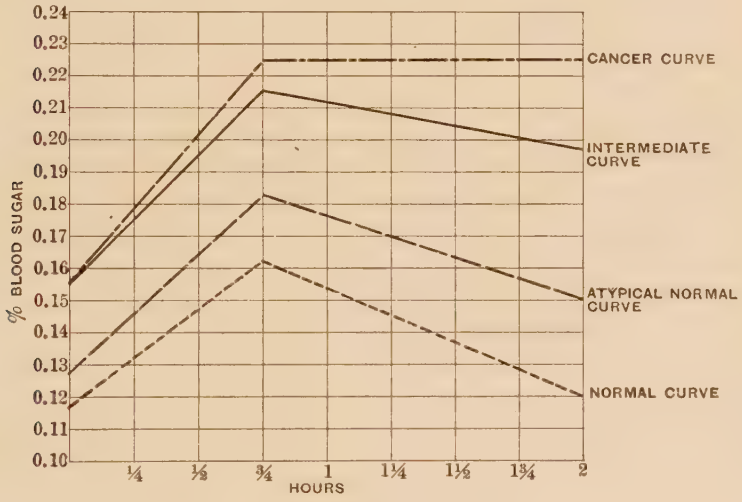

CHART V

4. THE CANCER CURVE. The cancer curve is usually observed in carcinoma of the gastro-intestinal tract in which even in the fasting state there is a high sugar content of from 0.14 to 0.17 per cent., followed after the ingestion of the 100 gm. of dextrose by an initial rise of from 0.21 to 0.24 per cent. or higher within 45 minutes, remaining at this level for at least 120 minutes, and at no time during this period falling below 0.20 per cent. This form of curve was observed in all of the cases of cancer of the gastro-intestinal tract, but was not present in any one of the other 55 examinations, including 5 cases of carcinoma outside of this tract nor in 2 cases of sarcoma nor in any of the 45 cases of benign affections of the gastro-intestinal tract. The form of curve present therefore in gastro-

intestinal cancer is rather characteristic and can usually be distinguished from that observed in cancer of any other region of the body or from that of non-malignant disease. It should be noted, however, that in cases of suspected carcinoma of the gastro-intestinal tract in which the curve is not absolutely characteristic or is of the intermediate type that a second examination made after a short interval of time will usually reveal the true condition.

TABLE PRESENTING THE PERCENTAGES OF BLOOD-SUGAR OBTAINED IN THE 32 CASES OF CANCER OF THE GASTRO-INTESTINAL TRACT.

No.	Name.	Cancer of	0 Hour.	45 Min.	120 Min.
1	M. J. B.	Pylorus	0.141	0.250	0.238
2	G. F. B.	Liver and stomach	.12	.198	.192
3	S. S. B.	Stomach	.163	.268	.278
4	T. C.	Liver and stomach	.147	.191	.194
5	G. C.	Liver and stomach	.162	.204	.201
6	M. H. C.	Liver	.196	.240	.243
7	D. E. D.	Stomach	.178	.364	.332
8	C. E. D.	Pylorus and lesser curvature	.131	.187	.183
9	J. A. D.	General carcinomatosis	.161	.258	.255
10	E. G.	Uterus and rectum	.125	.187	.194
11	D. G.	General carcinomatosis	.161	.250	.256
12	H. G.	Liver and stomach	.163	.214	.208
13	W. K.	Pylorus	.149	.198	.194
14	C. S. I.	Cecum	.155	.226	.258
15	P. J.	Pylorus	.142	.187	.179
16	F. L.	Rectum	.202	.300	.264
17	J. L.	Pylorus	.176	.252	.266
18	C. J. M.	Stomach	.158	.210	.210
19	H. C. P.	Stomach	.142	.262	.247
20	G. C. P.	Stomach	.164	.242	.238
21	M. M.	Pylorus	.138	.204	.204
22	R. E. M.	Stomach	.142	.194	.192
23	E. R.	Pylorus	.141	.192	.174
24	I. P. S.	Liver and stomach	.121	.162	.153
25	S. F. L.	Tongue	.384	.497	.497
26	M. S.	Cardia	.131	.180	.224
27	C. S.	Stomach	.206	.266	.256
28	J. T. T.	Pylorus	.171	.239	.240
29	S. V.	Liver and stomach	.139	.214	.206
30	S. W.	Pylorus	.162	.198	.194
31	E. W.	Stomach	.154	.192	.178
32	W. A. Z.	Stomach	.161	.220	.218

We have not had an opportunity to observe early cases of cancer of the gastro-intestinal tract according to this test except in a single instance, but we are under the impression that the test is quite as definite in early as in late cases, as it is usually positive whether

cachexia exists or not or whether there is but a slight or a marked involvement of the organs. It is important to note that diabetes, nephritis, tuberculosis and disturbances of the thyroid should always be excluded before the tolerance test is undertaken, inasmuch as hyperglycemia is frequently present in these affections. Inasmuch, however, as this test is to be utilized only as a means of differentiation between carcinoma and other diseases of the gastrointestinal tract, many conditions associated with hyperglycemia need not be taken here into consideration.

The value of the test is well illustrated in three of the cases of this series; we append a brief abstract of the histories of these cases:

Case I.—M. R. (No. 4857), male, aged fifty-four years, had been complaining of stomach trouble for some months; he was affected with nausea and vomiting; much discomfort after meals with eructations, flatulency, loss of appetite and loss of flesh (twenty pounds). Recently he had frequently vomited food taken the day previously. On physical examination the liver was found enlarged and there was a definite resistance in the upper right quadrant. The examination of the gastric contents revealed but small amounts of free hydrochloric acid, and there was marked retention. On roentgen-ray examination there was found an enormously dilated stomach, with a large filling defect and a 1080-minute retention. The diagnosis of pyloric obstruction, due to ulceration and possibly to a malignant growth, was made. The sugar tolerance test revealed a normal curve pointing definitely against carcinoma. At operation, performed February 21, 1920, by Dr. J. M. T. Finney, a nonmalignant pyloric stricture was found.

Case II.—E. S. (No. 5002), male, aged forty-eight years, had been affected with indigestion for the past six months. He had lost ten pounds in weight, had nausea, vomiting, loss of appetite and complained of weakness and of the passage of blood in the stools. On physical examination of the abdomen nothing abnormal was determined. His gastric secretion presented a true achylia. The stools contained occult blood and the roentgen-ray revealed a large filling defect at the pylorus, involving a large area on the lesser curvature. The diagnosis of carcinoma was made. The sugar tolerance test, however, presented a perfectly normal curve. At operation, March 1, 1920, by Dr. J. M. T. Finney, a chronic gastritis with pylorospasm was revealed.

Case III.—M. M. C. (No. 4652), male, aged sixty-one years, complained of indigestion for at least four years, which had recently become more aggravated; there was present loss of appetite, eructations of gas, pressure and fulness after meals, and loss of flesh (twenty pounds). On physical examination of the abdomen the liver was found enlarged; there were no palpable masses present. The gastric secretion presented a low total acidity 10 to 12, with an absence of free HCl. The roentgen-ray examination revealed a large filling defect at the pylorus and on the lesser curvature, on account of which a positive diagnosis of carcinoma was made. The sugar-tolerance test, however, presented an atypical normal curve. The Wassermann test was positive and the patient has recovered after having undergone an antiluetic treatment.

In considering the possible causes that may be responsible for the delayed tolerance curve in the blood in cancer, two possibilities have been suggested by Dr. Charles E. Simon:

1. Whenever increased cell production is maintained there must necessarily be some source of energy available, and inasmuch as the most potent source is dextrose, it is quite conceivable that a special call might be made on the part of the multiplying cells upon the liver for an increased supply of dextrose. Should the liver respond to this call, but owing to the defective blood supply in a carcinoma only a small portion of the available sugar should be utilized, a hyperglycemia might develop. This hyperglycemia does not occur in sarcoma, which may be explained on the basis that in this disease there is a more or less abundant blood supply, whereas in carcinoma the reverse is observed. The available dextrose in sarcoma would on this account be utilized and a hyperglycemia would consequently not develop.

2. As a second possibility one could conceive that a hormone might be liberated into the circulation by the carcinoma, in consequence of which the normal power of oxidation of the sugar on the part of the tissues at large or of certain special ones, like the muscle tissues, might be impaired; in consequence a hyperglycemia could not only result under normal conditions of carbohydrate supply but also when an increased quantity of dextrose is made available; in addition it might be possible that such a factor might be responsible for the defective nutrition of the body at large and thus for the progressive loss of weight associated with cancer.

From our study of the blood-sugar tolerance test in health, as well as in the various affections of the gastro-intestinal tract, we believe that the following conclusions may safely be drawn:

I. There is present in carcinoma of the gastro-intestinal tract usually a rather characteristic curve of sugar tolerance which differs somewhat from that observed in carcinoma of other regions of the body. The curve of this affection usually presents a high sugar content even in the fasting state, followed by an initial rise up to 0.24 per cent. or higher within 45 minutes after the ingestion of the dextrose remaining at this level for at least 120 minutes, and at no time during this period falling below 0.20 per cent.

II. The sugar tolerance test is rather distinctive, so that it may render valuable assistance in a large proportion of cases as a means of differential diagnosis between carcinoma and other diseases of the gastro-intestinal tract.

III. The opportunity has not been afforded to test a sufficient number of early cases of cancer of the stomach and intestines according to this method, so that as yet the value of this test as a means of early diagnosis has not been established; nevertheless, as positive curves occur equally whether cachexia exists or not, or whether the extent of the involvement be slight or great, we are under the impression that the results may be quite definite even in the early cases of the disease. This question, however, requires further study.

IV. Finally, while we fully realize that this test is not specific of carcinoma and cannot be relied upon alone without entering into the clinical aspects of the disease, and that there are cases of carcinoma in which negative findings occur or non-malignant conditions in which the results are positive, nevertheless we are of the opinion that when properly performed the blood-sugar tolerance test may be of considerable diagnostic help in obscure cases of carcinoma of the gastro-intestinal tract.

EPINEPHRIN HYPERSENSITIVENESS AND ITS RELATION TO HYPERTHYROIDISM

By FRANCIS W. PEABODY, CYRUS C. STURGIS, EDNA M. TOMPKINS

AND

JOSEPH T. WEARN

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There are at the present time two procedures in extensive use in this country for the determination of functional hyperactivity of the thyroid gland. One of these, the measurement of the basal metabolism, rests on sound experimental and clinical observations, for there is abundant evidence that stimulation of the thyroid gland, or administration of its active principle, induces an increase in heat production. There can be little doubt that stimulation of metabolism is an important feature in hyperthyroidism and that the measurement of the metabolism is a valuable index of the degree of activity of the thyroid gland, but we are still in the dark as to how far other associated features combine with this and go to make up the clinical symptomatology of hyperthyroidism. The outstanding drawback to this method for the determination of thyroid activity is that, even with the recently simplified technical procedures, it requires specialized training and experience both for its application and for the proper interpretation of the information derived from it.

The second procedure consists of the injections of epinephrin and its diagnostic significance depends on the type of reaction which has been described as occurring in patients with hyperthyroidism, and which is supposed to be characteristic of this condition. The test is usually carried out by the method suggested by Goetsch,

and 0.5 c.c. of a 1 to 1000 solution of epinephrin is administered.[1] * The "positive" reaction which has been assumed to indicate hyperthyroidism consists of the production of a rise of systolic blood-pressure of at least 10 mm. of mercury, or a rise in pulse-rate of at least 10 beats per minute, together with an increase of such signs and symptoms as tremor, sweating, vascular pulsation, nervousness and palpitation.

The test is so easy to apply and apparently so simple to interpret that it has been widely adopted as a diagnostic measure, and the "positive" reaction is frequently considered as an indication even for surgical interference. On account of this tendency to regard the test as highly specific in its significance, it has seemed to be of

* The tests were actually carried out in the following manner, as described by Wearn and Sturgis (Arch. Int. Med., 1919, xxiv, 247): "The patients remain at absolute rest in bed for a period of one hour. If there is restlessness or apprehension they should be reassured, and every effort made to obtain mental as well as physical quiet. At the end of the rest period control readings of the blood-pressure, pulse- and respiratory rates are made at five-minute intervals. Also at this time a note is made as to the presence of nervousness, precordial pain, dizziness, palpitation or any other symptoms which may be significant. Likewise the objective condition of the patient is observed, and it is recorded if any of the following signs are present: tremor of the hands, sweating, coldness of the hands, throbbing of the neck, epigastrium, or over the precordium and pallor or flushing. At the end of an hour's rest in bed the patient is usually quiet and has few complaints; the blood-pressure and heart-rate are normal, or there may be a slight tachycardia (in sharp contrast to the patient with exophthalmic goiter in whom a more marked tachycardia persists even when at rest in bed). Likewise after the rest period there is little to record from an objective or subjective standpoint. If this condition approaching the normal has not been attained then the control readings should continue further, for with nervousness, tremor, sweating, tachycardia, or possibly other prominent signs already present it would be difficult to judge the effect of the epinephrin. In a few patients the control readings of blood-pressure and pulse remained at a level slightly above the normal, but the injection of epinephrin was carried out after they became constant. In a number of patients venipuncture was done at the end of the rest period for blood-sugar determinations, but when this or any other disturbing factor is introduced it is necessary that subsequent control readings be made, and these should agree with the preliminary readings before the test can proceed.

After satisfactory control readings have been made, 0.5 c.c. of a 1: 1000 solution of epinephrin, freshly prepared, is injected deep into the deltoid muscle. In all of these tests the solution was made by adding $\frac{1}{30}$ grain of Parke, Davis & Co. adrenalin brand of epinephrin tablet to 1 c.c. of water, thereby making a 1 : 1000 solution.

After the injection four or five readings are made of the blood-pressure, pulse- and respiratory-rates at two- or three-minute intervals, and also at these times any change in the objective or subjective condition of the patient is noted. After the first few observations, readings are continued at five-minute intervals until one hour after the injection, when ten-minute readings are made for a period of one-half hour, thus making the observation period one and one-half hours from the time of the injection. From our experience at Lakewood it would seem that the time of observation could safely be cut to one hour, as we have failed to observe anything of importance after that length of time."

importance to study in more detail the nature of the reaction to epinephrin and to determine the conditions under which the "positive" reaction, which may be assumed to indicate epinephrin hypersensitiveness, appears. Such studies have been carried on at U. S. Army General Hospital No. 9, Lakewood, N. J., and at the Peter Bent Brigham Hospital, Boston. The present communication is a brief summary of the results.

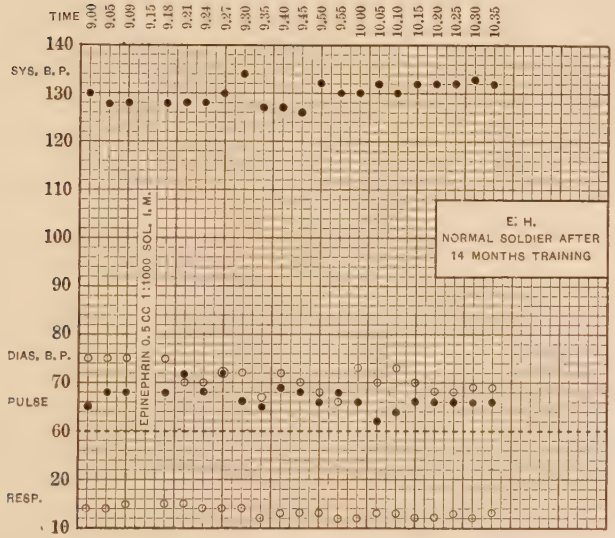
As far as is known, the difference between "positive" and "negative" reactions to epinephrin is a quantitative one, and what clinical significance the test possesses depends on the selection of a proper differentiating dose. Even so small an amount as that used (0.5 c.c. of a 1 to 1000 solution) probably produces some effect in everyone. In subjects reacting wholly "negatively" it has been found that the basal metabolism is temporarily raised from 5 to 15 per cent., while in those reacting "positively" the increase is from 15 to 30 per cent.[2] No such effect is observed, even in nervous subjects, from the prick of a needle or from the injection of salt solution. Under given circumstances the effect of the drug seems to remain fairly constant in a given individual.

A fundamental part of the investigation obviously consists of the "control" observations carried out on normal individuals. These were begun in the army and it was soon found that the problem was complicated by the fact that our standards of normality were not clearly defined. A number of patients in the hospital for minor surgical ailments turned out to be hypersensitive to epinephrin. Analysis of their past histories and of their characters suggested that while they were normal men judged by the usual standards, they were not the types from which good soldiers are made. From the point of view of the army, the "normal control" must be the soldier who can withstand the strain of hard training. A group of 26 men from an organization which had undergone training for fourteen months and was on its way overseas were therefore studied and none of these were found to give "positive" reactions to epinephrin. These were, of course, selected normals for they were men of unusual physical endurance and nervous stability. A second group of normal men tested consisted of 28 Harvard medical students, and among these 4, or 14

per cent., gave perfectly definite "positive" reactions. Four other men showed transient rises of pulse-rate of over 10 beats per minute, or of a systolic blood-pressure of more than 10 mm., or both. But

CHART I.

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	HANDS	MISCELLANEOUS
9.00	–	–	–	–	COLD	RESTING QUIETLY
9.05	–	–	–	–	,,	,, ,,
9.09	–	–	–	–	,,	,, ,,
9.15	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY					
9.18	V. SL.	–	–	–	COLD	RESTING QUIETLY
9.21	–	–	–	–	,,	,, ,,
9.24	–	–	–	–	,,	,, ,,
9.27	–	–	–	–	,,	,, ,,
9.30	–	–	–	–	,,	,, ,,
9.35	–	–	–	–	,,	,, ,,
9.40	–	–	–	–	,,	,, ,,
9.45	–	–	–	–	,,	,, ,,
9.50	–	–	–	–	,,	,, ,,
9.55	–	–	–	–	,,	,, ,,
10.00	–	–	–	–	,,	,, ,,
10.05	V. SL.	–	–	–	,,	,, ,,
10.10	+	–	–	–	,,	,, ,,
10.15	+	–	–	–	,,	,, ,,
10.20	+	–	–	–	,,	,, ,,
10.25	+	–	–	–	,,	,, ,,
10.30	+	–	–	–	,,	,, ,,

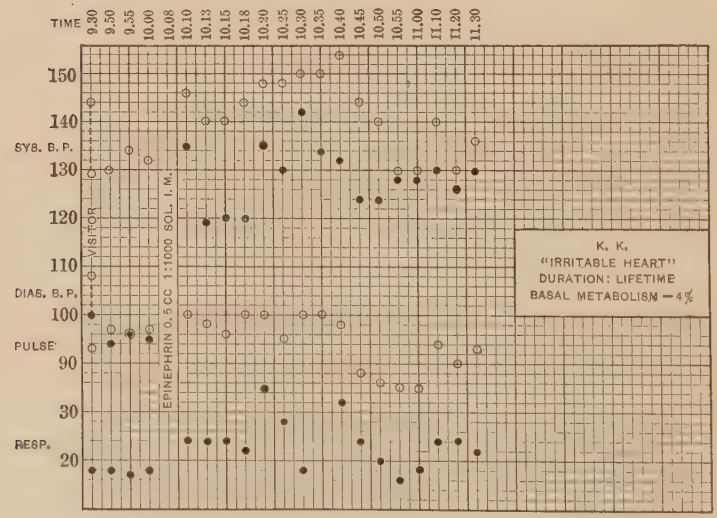


as these were usually noticed only on one observation and not accompanied by the characteristic symptoms they were not regarded as giving "positive" reactions. In many other "negative" cases

slight increase in blood-pressure and pulse-rate were noted. In addition to this there is a third group which may also be properly considered among the normals. These were patients at General Hospital No. 9, on whom the diagnosis of "effort syndrome" was

CHART II.

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	MISCELLANEOUS
9.30	+	+	+	−	QUIET - EASILY DISTURBED BY VISITORS
9.50	+	+	+	−	"
9.55	+	+	+	−	"
10.00	+	+	+	−	"
10.08	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY				
10.10	++	++	+	+	SLIGHT RESTLESSNESS
10.13	++	++	+	+	RESTLESS
10.15	++	++	+	+	SHORT OF BREATH - PALPITATION
10.20	+++	+++	++	+	TWITCHING OF ARM AND CHEST MUSCLES
10.25	+++	+++	++	+	RESTLESS - NERVOUS - TWITCHING
10.30	+++	+++	+	+	DEFINITE REACTION
10.40	+++	+++	+	+	QUIETER - STILL VERY RESTLESS
10.45	+++	+++	+	+	TWITCHING LESS
10.50	++	++	+	+	QUIETER
10.55	++	++	+	+	"
11.00	++	++	+	+	"
11.10	++	+	+	+	QUIET
11.20	++	+	+	+	"



made—men who, for the most part, would pass in civil life as within the bounds of normality but who developed symptoms, usually of a psychoneurotic nature, under the nervous and physical strain of army life. The exact nature of this condition is still uncertain,

but there is very general agreement that hyperthyroidism plays no part in it. The clinical picture is not similar to that of hyperthyroidism; the subjects improve under therapeutic measures that make patients with hyperthyroidism worse; and the basal metabolism is normal. If so common a condition as "effort syndrome" represented even a mild or incipient type of hyperthyroidism it is almost inconceivable that definite cases should have been so rare in the army. Among 143 cases of "effort syndrome" 69, or 48 per cent., reacted "positively" to the epinephrin test. These results are not unlike those obtained by Boas,[3] who reports that 28 per cent. of 21 cases of "effort syndrome" gave "positive" reactions. In association with this type of subject one may also consider the observations made on a small number of definite psychoneurotics—individuals who cannot be classed as wholly normal because the symptoms arising in the course of a normal life induced them to seek medical advice, but persons, on the other hand, in whom no evidence of organic disease, either of the thyroid gland or of any other organ could be found. Among 7 such subjects all were found to give "positive" reactions to epinephrin.

Summarizing the observations made on the various groups of subjects without evidence of organic disease, one finds that hypersensitiveness to epinephrin is certainly not characteristic of the hardened soldier, that it occurs in about 14 per cent. of average young men, such as medical students, that it is present in nearly 50 per cent. of the type of young men who broke down under military training with the picture of "effort syndrome," and that it is still more common among definite psychoneurotics. It is difficult not to see some relation between epinephrin hypersensitiveness and what one may call a "nervous constitution." On account of what is generally accepted as being known about the physiological action of epinephrin one is tempted to regard the test as indicating a hypersensitiveness of the sympathetic nervous system. It is frequently possible to select, on the basis of clinical study, the subjects who will react to epinephrin, but this is by no means always the case. Even after considerable experience with the test one is liable to fall into error. There are many highly "nervous" or "neurotic" people who do not react "positively,"

and there are occasional persons who have no apparent neurotic tendencies who react violently to the drug.

The epinephrin test has also been used on various other types of hospital case. Among 17 patients with organic heart disease 3, or 17 per cent., gave "positive" reactions. This corresponds closely with the 14 per cent. of "positive" reactions found in the group of medical students, and it is possible that the figure represents approximately the average incidence of the reaction among normal persons. Incidental observations have also been made on cases of syphilis, chorea, asthma, acromegaly, epilepsy, diabetes, dementia precox, and hyperthyroidism and one or more "positive" results have been obtained in each condition. In a series of 21 patients who were convalescent from acute infections 12, or 57 per

TABLE I

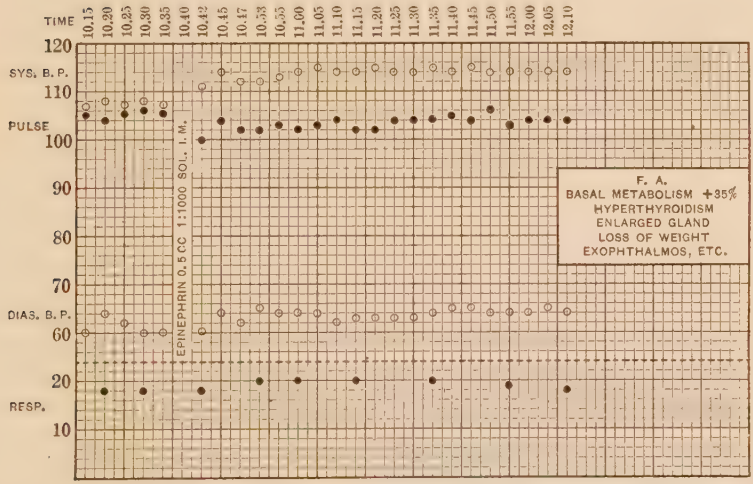
Case.	Disease.	Positive.	Negative.	Doubtful.
2	Pneumonia	2	0	0
3	Diphtheria	2	1	0
9	Acute rheumatic fever	4	4	1
1	Acute tonsillitis (tonsillectomy)	1	0	0
6	Scattered	3	3	0

cent., gave "positive" reactions—a figure in close agreement with results obtained by F. M. Smith,[4] who found that 50 per cent. of 50 cases following influenzal pneumonia reacted "positively." Nicholson and Goetsch[5] report 19 "positive" reactions among 40 cases of questionable or definite tuberculosis, a percentage incidence of 47. One case observed at General Hospital No. 9 seems particularly worth noting. A boy with an organic heart lesion, but otherwise normal, gave a "negative" test. A few days later he had an attack of acute tonsillitis which was followed by a tonsillectomy. A repetition of the test, after convalescence from the operation, gave a "positive" result. This evidence certainly suggests that infections may induce a hypersensitiveness of the sympathetic nervous system, and there are, of course, various clinical symptoms which are in harmony with such a conception. To assume, however, that there is necessarily an associated hyperactivity of the thyroid gland seems quite unwarranted, if only for the reason that many of these postinfectious cases improve with

graduated exercises, a type of treatment wholly unsuited to patients with hyperthyroidism. It is true that in certain cases with hyperthyroidism the condition has apparently manifested itself after some acute infectious disease, but the reverse is still more striking

CHART III

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	HANDS	MISCELLANEOUS
10.15	++	++	++	+	COOL	ONLY FAIRLY QUIET-MOVES ARMS AND HEAD
10.25	++	++	++	+	,,	,, ,, ,, FEW MOVES
10.35	++	++	++	+	,,	,, ,, ,, ,, ,,
10.40	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY					
10.41	+++	++	++	PALE	COOL	NO CHANGE
10.44	++	++	++	PALLOR GONE	,,	,, ,,
10.48	++	++	++	+	,,	,, ,,
10.57	++	++	++	+	,,	THINKS HER HEART IS BEATING FASTER
11.02	++	++	++	+	,,	NOTICES NOTHING ELSE
11.07	++	++	++	+	,,	FAIRLY QUIET
11.14	++	++	++	+	,,	,, ,,
11.22	++	++	++	+	,,	,, ,,
11.28	++	++	++	+	,,	,, ,,
11.38	++	++	++	+	,,	,, ,, NO SIGN OF REACTION
11.44	++	++	++	+	,,	,, ,,
11.52	++	++	++	+	,,	,, ,,
12.02	++	++	++	+	,,	,, ,,
12.08	++	++	++	+	,,	,, ,,

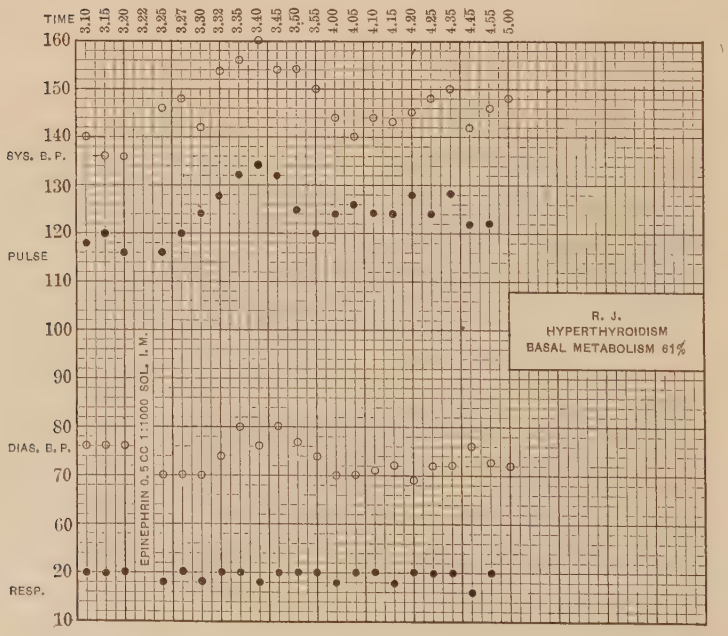


for the development of outspoken hyperthyroidism after acute infections is without question more rare than it would be if there were stimulation of the gland in nearly one-half of the cases of acute infectious disease.

Special attention has been paid to the epinephrin test in hyperthyroidism. The diagnosis in the cases reported on was based on the classical signs and symptoms and the history, together with

CHART IV.

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	MISCELLANEOUS
3.15	++	++	+	++	VERY RESTLESS - MOVING CONSTANTLY
3.20	++	++	+	++	" " " "
3.22	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY				
3.25	++	+	+	SL. PALLOR	RESTLESS AND MOVING
3.30	++	+	++	++	RESTLESSNESS INCREASING
3.32	+++	++	+++	+++	NERVOUS, EXCITED, THROBBING
3.35	+++	+++	+++	+++	NERVOUSNESS INCREASING, APPREHENSIVE
3.40	+++	++++	+++	+++	MARKED REACTION
3.45	+++	+++	+++	+++	SOMEWHAT QUIETER
3.50	+++	+++	+++	+++	" "
4.00	+++	+++	+++	+++	" "
4.05	+++	++	++	++	NERVOUSNESS DECREASING
4.15	++	++	++	++	" "
4.25	+++	++	++	++	" "
4.45	+++	+	++	++	" "
4.55	+++	+	++	++	STILL MORE RESTLESS THAN AT START



the determination of the basal metabolism. Twenty-one cases have been studied and in 15, or 71 per cent., "positive" reactions

were obtained; 6 unquestionable cases, 4 in early stages and 2 in later stages, with basal metabolism ranging between 21 and 35

CHART V.

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	HANDS	MISCELLANEOUS
9.50	+	+	−	+	WARM	QUIET
9.55	+	+	−	+	"	"
10.03	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY					
10.05	++	++	−	+	WARM	QUIET
10.07	+++	+++	+SL.	SL. PALLOR	COOL	RESTLESS AND NERVOUS
10.10	+++	+++	+	+	"	MORE RESTLESS AND GENERALLY NERVOUS
10.15	+++	+++	+	+	"	" REACTION INCREASING
10.20	++++	++++	+	+	"	" "
10.25	++++	++++	++	+	WARMER	GENERALLY UNCOMFORTABLE
10.30	++++	++++	++	+	"	
10.35	++++	++++	++	+	"	REACTION NOW MARKED PALPITATION, RESTLESSNESS, VERY NERVOUS, FEELS QUEER
10.40	++++	++++	++	+	"	NUMEROUS EXTRA SYSTOLES
10.45	++++	++++	++	+	"	REACTION CONTINUES
10.50	++++	++++	++	+	"	" "
10.55	++++	++++	++	+	"	
11.00	++++	++++	++	+	WARM	
11.05	++++	++++	++	+	"	BEGINNING TO FEEL BETTER QUIETER
11.15	++++	++++	+	+	"	HEART ACTION REGULAR FEELS "FINE"
11.25	++++	++++	+	+	"	
11.35	++++	++++	+	+	"	NOW FEELS COMFORTABLE

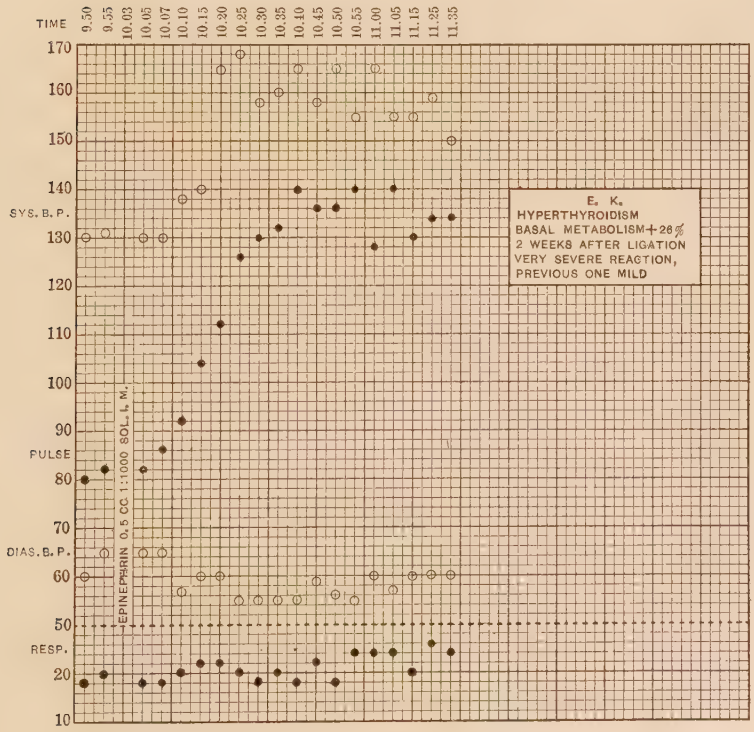


CHART V

per cent. above normal, gave "negative" epinephrin reactions. No relation was noted between the intensity of the reaction to epinephrin and the apparent severity of the case. One patient with a basal metabolism 61 per cent. above normal, was considered to be extremely toxic but gave a comparatively slight reaction, while a mild case, with a basal metabolism 26 per cent. above normal, gave a very severe reaction. Nine patients were tested on whom thyroidectomies had been done two or three years previously and who had been living normal lives without symptoms for a year or more. Five of them gave "negative" reactions, while 4, in whom the basal metabolism was −18 per cent., −15 per cent., −1 per cent. and +12 per cent., gave "positive" reactions.

The general conclusions which it seems justifiable to draw from our observations are as follows:

1. Different individuals, both sick and well, react with different degrees of intensity to the injection of epinephrin. By means of selected dosage of the drug and carefully chosen criteria for the response, one can differentiate, somewhat artificially, between the slight reactions which are called "negative" and the more violent reactions which are called "positive." In certain instances "doubtful" or "questionable" reactions are obtained.

2. The fundamental nature of the reaction is unknown. It is associated with a rise in heat production which runs more or less parallel to the intensity of the reaction. On the basis of what is definitely understood with regard to the physiological action of epinephrin it seems probable that the phenomenon is due to a stimulation of the sympathetic nervous system. Theoretically, a "positive" reaction might indicate hyperactivity of the thyroid glands, of the adrenal glands, or of the sympathetic nervous system. It might, on the other hand, depend on a lowered threshold of response of the sympathetic nervous system. With the exception of hyperthyroidism, little is known about these conditions in man, but they probably occur and there would seem to be no reason for assuming that a "positive" epinephrin reaction is constantly associated with hyperthyroidism. It is much more likely that different causes account for the reaction in different types of clinical cases.

3. Hypersensitiveness to epinephrin is found in many patients with the clinical picture of hyperthyroidism and with an increased basal metabolism, but it is not constant under these conditions.

4. Hypersensitiveness to epinephrin is also found in persons who have no indications of hyperthyroidism. Thus it was present in many psychoneurotics, in about 50 per cent. of patients convalescent from acute infections, in nearly the same proportion of soldiers with "effort syndrome," in 14 per cent. of apparently normal young men, and in patients with various unrelated diseases.

5. The "positive" reaction to epinephrin appears to occur most often in highly nervous individuals but it is not constant in such persons. The clinical significance of the reaction is not clear, but at present it should certainly not be regarded as having any specific significance in the diagnosis of hyperthyroidism.

DISCUSSION

Dr. M. H. Fussell, of Philadelphia, said that he was very pleased to hear these observations on the soldier with effort syndrome. The so-called Goetsch test had been widely accepted as a positive indication of hyperthyroidism. The unreliability of such a conclusion was now shown. Dr. Fussell said he had a patient who gave a very active reaction to the Goetsch test, but the basal metabolism was not above normal. He had nervousness and tachycardia, and he had asked to be operated upon, on the ground of a positive Goetsch test.

Dr. L. G. Rowntree, of Rochester, asked if these hyperthyroid cases were of the Graves' type, or were they toxic adenomata? Was there any difference between the toxic type and the exophthalmic type?

Dr. F. W. Peabody, of Boston, replying to Dr. Rowntree, said that only two of the cases were adenomata. He was glad to hear that the clinical experience of others agreed with theirs. He had begun to feel that placing reliance on the test was pretty dangerous.

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ACUTE INFECTIOUS MYOCLONUS MULTIPLEX AND EPIDEMIC MYOCLONUS MULTIPLEX (EPIDEMIC ENCEPHALITIS)[1]

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As acute infectious myoclonus multiplex I would direct attention to an unusual clinical type of acute infection of the nervous system which may appear both in sporadic and in epidemic form. The isolated or sporadic form is quite rare. Epidemic myoclonus multiplex, on the other hand, has been of frequent occurrence during the last winter and represents a special type of the epidemic encephalitis.

Symptomatology. The onset of the disease is acute and is characterized by sharp shooting pains in the trunks and extremities, at first local but rapidly becoming generalized. They may reach an extreme degree of intensity. Spinal pains are sometimes present but are not nearly so intense as in the more peripheral areas.

The pains are soon followed by the pathognomonic muscle jerks, waves and twitchings (myoclonus and myokymia multiplex) that characterize the affection. The muscle contractions follow in the wake of the pain and make their appearance in those parts where the pains were first manifested. In some cases an interval of a week may elapse before the appearance of myoclonus and myokymia. The twitchings are bilateral and multiple, and may be generalized. A tendency to localization in certain regions of the body may occur, the muscles of the abdomen and lower extremities showing an especial vulnerability. The contractions are of quick clonic character,

[1] Preliminary report to the New York Neurological Society, March 2, 1920, and the Association of American Physicians, May 4, 1920.

involving individual muscles or portions of muscles, but not synergic groups, so that the resulting locomotor effect is comparatively slight.

In many of the cases there is well marked delirium, which varies in duration and intensity with the severity of the infection. In milder types there may be only irritability, restlessness and insomnia associated with anxiety and apprehension. The myoclonus delirium presents the characteristics of a toxic delirium, and is characterized by hallucinations, illusions and transitory delusions. There are restlessness, insomnia, apprehension, disconnected thought and mental confusion. The symptoms are all more conspicuous at night, and the delirium content frequently takes on an occupation form. In the graver cases there is an attention disorder with symptoms of Korsakoff's syndrome. In the late stage there may be apathy and a tendency to stupor.

During the course of the disease there is moderate fever, acceleration of the pulse, and often hyperhidrosis. The degree of sweating seems to bear a relation to the activity of the muscular phenomena. There is no tenderness of the nerve trunks, but during the painful stage there is general sensitiveness to movement and surface impressions (hyperesthesia). The myotatic irritability of the affected muscles may be increased, and there is sometimes an exaggeration of the normal idiomuscular response (myoidema).

There is no paralysis or paresis of any muscle or group of muscles. The sensory disturbances are chiefly irritative in character, consisting of pain, hyperesthesia and occasional paresthesias in the distal parts of the extremities. There is no anesthesia in the usual sense, and only rarely a diminished sensibility to pain during the acute stage of the disease. There is no ataxia and no loss of the deep sensibility. The tendon reflexes are usually present and active. Occasionally, in the late stages the Achilles-jerks and the knee-jerks are diminished or not elicitable.

There are no other evidences of organic disease of the nervous system, and the clinical picture is characterized by myoclonus and myokymia multiplex, lancinating pains and delirium. The mode of onset and course of the disease are suggestive of an infectious process with limited, selective involvement of the central nervous system.

The relationship of the epidemic form of myoclonus multiplex to

epidemic encephalitis is shown not only by its prevalence at the same time, but also by various combination forms (cranial nerve palsies and myoclonus) which have been encountered. And there is little doubt that all of these various types are related to the same etiologic factor; whether this be true of the sporadic type of myoclonus multiplex is, I believe, still an open question.

Paramyoclonus Multiplex and Myokymia. The peculiar nature of the motor disorder which these cases present is well recognized in neurologic literature, and is described under such headings as paramyoclonus multiplex,[1] myokymia[2] and myoclonus fibrillaris multiplex.[3] They are all to be regarded as representing varying degrees of a fundamental type of motor disorder, referable to the lower motor neurons.

A variety of etiologic factors have been recognized. Among these may be mentioned shock, exhaustion, exposure to cold, diabetes, lead poisoning, trauma and alcoholism. Myokymia has also been recorded as a late sequela of sciatica and poliomyelitis. Similar muscular phenomena have also been observed in the course of certain infectious diseases,[4] as diphtheria, malaria and acute articular rheumatism.

Paramyoclonus multiplex and myokymia are not to be confused with myoclonia of the cortical type. Cortical myoclonia is a motor disorder which affects synergic groups of muscles and produces considerable locomotor effect. It resembles much more in the character of movements produced, the chorea or tic convulsif, and is readily differentiated from myoclonus of the spinal type. This is characterized by involvement of individual mucles or portions of muscles which, as such, are not voluntary control.

Myoclonus multiplex, myokymia and muscle fibrillation are therefore referable to the spinal level of the central nervous system and are to be sharply distinguished from myoclonic manifestations of cerebral origin.

[1] Friedreich: Paramyoclonus Multiplex, Virchows Arch. f. path. Anat., 1881, lxxxvi, 421.

[2] Schultze, F.: Beiträge zur Muskelpathologie (Myokymia), Ztschr. f. Nervenh., 1894, vi, 65, 167.

[3] Kny: Ueber ein dem Paramyoclonus multiplex (Friedreich) nahestehendes Krankheitsbild, Arch. f. Psychiat., 1888, ix, 577.

[4] Cited by Eichhorst: Spezielle Pathologie und Therapie, 1907, iii, 553.

Pathology has thrown very little light on the localization and nature of these motor disorders. They are evidently irritative manifestations resulting from direct or reflex excitation of the peripheral motor neurons, the exact seat of which cannot be determined with any degree of certainty in the present state of our knowledge.

The nervous system of Friedreich's original case of paramyoclonus multiplex was subjected to careful pathologic study by Schultze[1] with quite negative results. Some years later I[2] had an opportunity of studying the nervous system of paramyoclonus multiplex (Friedreich's type) by modern histologic methods. No lesions of the nervous system were found that explained the peculiar motor phenomena of this disease. There was, however, some hypertrophy of the muscle fibers which was regarded as an effect and not a cause of the disease.

When one considers the frequency of meningeal, radicular, ganglionic and other forms of spinal and peripheral nerve irritation, in which there are no evidences of myoclonus or myokymia, it would appear hazardous at the present time to attempt a more definite localization of the disorder than as irritative manifestations referable to the spinal level of motility.

Nine cases of infectious myoclonus multiplex have come under my observation during the last sixteen years, two sporadic cases, one in 1904, and another in 1914. The remainder were of the epidemic type and occurred during the recent epidemic of lethargic encephalitis.

Report of Cases

The Sporadic Type

Case 1.—*History.* In 1904, while engaged in the pathologic study of a case of paramyoclonus multiplex, I saw in Bellevue Hospital, through the courtesy of Dr. C. L. Dana, this unusual case. It was that of a young man who had been admitted to the ward in delirium and who presented generalized twitchings and quiverings of the skeletal muscles. These had been preceded by pain. The muscular contractions were similar to those

[1] Ueber den Paramyoclonus multiplex (Friedreich), Neurol. Centralbl., 1886, xvi, 363.

[2] Hunt, J. R.: A Contribution to the Pathology of Paramyoclonus Multiplex (Friedreich Type), Jour. Nerv. and Ment. Dis., 1903, xxx, 408.

described in cases of paramyoclonus multiplex and myokymia, and were characterized by clonic contractions, muscle waves and fibrillations, producing but slight locomotor effect and not involving synergic groups. They continued during the entire course of the disease, which terminated fatally about a month after admission.

Course. During this period there was moderate fever, which rose in the later period of the disease. There were no evidences of organic disease of the nervous system other than the myoclonusmyokymia multiplex and the delirium. The reflexes were normal; there were no paralyses and, so far as could be determined, no anesthesias. The delirium was quite active at first, requiring restraint and later passing into stupor. No definite history of the mode of onset could be obtained, excepting that it was acute, and accompanied by pain. The symptoms appeared only shortly before admission, and careful clinical and laboratory examinations at the time failed to throw any light on the nature or origin of the delirium and the myoclonus.

Histologic Examination. After death a necropsy was performed, and this failed to show any gross lesions of the visceral or nervous system, other than those secondary to an acute infection. The case caused considerable interest and comment at the time, but was finally disposed of as myokymia occurring in the course of an obscure infection. Through the courtesy of Dr. Dana, the nervous system and some of the muscle tissue were placed at my disposal for microscopic study. Histologic examinations were made of portions of the cerebral cortex, of the brain stem, the spinal cord and peripheral nerves and muscles, and no lesions were found other than the acute cellular changes characteristic of infection. It was especially noteworthy that the anterior horn cells were in a very good state of preservation; only an occasional cell showed chromatolysis and eccentric position of the nucleus. There were no hemorrhagic or inflammatory foci and no meningeal reaction. The peripheral nerves and muscles revealed no special evidence of disease, and no pathologic lesions were found which would explain the existence of the curious motor disturbance, which at the time (sixteen years ago) was regarded as a toxic, irritative manifestation of the lower motor neurons.

A number of years later, in 1914, I saw at the Neurological Institute with Dr. Pearce Bailey another case of similar nature. I am indebted to Dr. Bailey for the privilege of reporting this case.

Case 2.—*History.* A salesman, aged thirty-seven years, married, and of Irish extraction, was admitted to the Neurological Institute, April 14, 1914, with generalized muscular twitchings, which were diagnosed as paramyoclonus multiplex. The affection began six weeks previously, with very severe pains in the back and legs, following a severe exposure in a snow

storm. The pains were so severe that it was difficult for him to find relief in any position. They lasted several days, and then gradually subsided, leaving in their wake curious twitchings and spasmodic contractions of the muscles and a feeling of general weakness. At the time of onset the family physician reported a moderate elevation of temperature (about 100° F.), rapid pulse (120) and a tendency to delirium at night.

The man's previous history was negative, save for pneumonia at the age of 15, and typhoid fever at 22; venereal disease was denied. There was no history of trauma, mental or physical. The patient had been quite moderate in the use of tobacco and of alcohol. There was no history of any alcoholic excesses.

Examination. On admission, there was a state of general muscular weakness, but no actual paralysis of any group of muscles. The gait and station were rendered slightly uncertain by the muscle jerks and quiverings, but there was no actual ataxia, either static or locomotor. There was a tremor of the hands and the fingers, and clonic contractions and quiverings of the muscles of the forearm. There was no ataxia of the upper extremities.

In both lower extremities, but especially in the muscles of the calf, there was a constant flow of fine and coarse muscular movements. These were wavelike in character, and were plainly visible, involving not only the finer fiber bundles (fibrillation) but also the larger groupings so that fascicular contractions were produced (myokymia); at times the whole muscle was involved in the contraction (myoclonus).

As a result of these movements the feet and legs were in a state of slight constant unrest, as the muscle twitchings were sufficiently forcible to flex and extend the toes, and produce other slight movements of the foot. While these movements were most pronounced in the calf muscles, they were nevertheless present in the muscles of the sole of the foot, and to a lesser degree in the quadriceps, the hamstring muscles and the glutei. The muscles of the back and shoulder girdle showed occasional rapid contractions beneath the skin. At times these contractions followed one another in rapid succession with as great an activity as in the lower extremities. Similar movements were also to be seen in the deltoids, and in slighter degree in the pectoral muscles. The muscles of the arm and hand were only slightly affected. In the recumbent posture the abdominal muscles were the seat of spasmodic and wavelike contractions, similar to those noted in the lower extremities.

The cranial nerves were normal. Articulation at times appeared to be slightly affected, although no definite signs of muscle twitching were visible in the face or tongue. The tendon reflexes were elicitable, and equal on both side. The knee-jerks and Achilles-jerks were normal, as were the triceps, biceps and supinator jerks of the upper extremities. The abdominal and cremasteric reflexes were present, but diminished. The plantar reflex

was of the flexor type. There was no Babinski reflex. When the skin was stroked there was developed a distinct tendency to dermographia. There was also a marked hyperhidrosis, which continued during the entire course of the disease. All sensation, both general and special, was normal.

Ophthalmologic examination, by Dr. Ward Holden, was negative. The vision was 20/20 in each eye. Pupils were equal, and responded normally to light and accommodation. There were no fundus changes. The heart and lungs were normal.

April 16, blood count revealed: red cells 4,912,000; hemoglobin, 91 per cent.; white blood corpuscles, 19,200; differential count: neutrophils, 60 per cent.; small lymphocytes, 28 per cent.; transitionals, 1 per cent.; large lymphocytes, 10 per cent.; eosinophils, 1 per cent. The Wassermann test of the blood was negative.

April 21, the Wassermann test of the spinal fluid was negative; globulin content, negative; 6 cells per cubic millimeter; Fehling's reduction, positive; blood culture, negative.

April 14, the specific gravity of the urine was 1.026. It was acid. No albumin, sugar, excess of indican, casts or blood was noted.

Examination of the feces was negative.

Subsequent Course. The patient remained in the hospital from April 14 to May 9, 1914. During this time there was no fever; the pulse was rapid, and ranged from 115 to 120. The systolic blood-pressure curve ranged from 160 to 180. Respirations ranged from 20 to 30 to the minute.

During the entire period of observation in the hospital and up to the time of the patient's discharge, there was a distinct tendency to delirium. He was restless and nervous, continually getting out of bed, and showing evidences of apprehension at night. It was difficult to restrain him. At times he was noisy and would shout; he would hold imaginary conversations with people, talked to himself, and thought that people were in the room with him. During the day he was quieter and much more manageable, but at night the delirium would come on, and he would become restless, excited, see faces and imaginary people in the room, and would hold imaginary conversations during the greater part of the night. At such times he perspired very freely. One night he had a sense of pressure and of a heavy weight on his chest and thought that some one was throwing something down on him. During this period there was constant insomnia, and he was confused and talked irrationally. On other occasions he would become rather troublesome and threatening with the nurses so that restraint was necessary. Once he thought he had spikes in his head and tried to pull them out. In the morning these symptoms would usually clear up and he was much brighter. On another occasion he said he must have his clothes: that he was going to Chicago on the first express train to transact important business. He spoke of having some kind of a bug in his head, but could

not think of the correct name of it. He said they would go around in circles, and stretched a piece of rubber until it snapped. He said he knew of a man in Chicago who had invented a machine for killing these bugs—that the bugs would put their heads in the hole of the trap, and immediately their heads would be burned off. This condition of nocturnal delirium and slight mental confusion continued during the entire period that he was in the hospital. He was a restless and rather troublesome patient and difficult to manage. He was discharged, May 24, slightly improved. The mental condition was better, and the muscular movements had diminished in frequency and intensity.

Subsequently his family physician reported that five months after his discharge he returned to work, having gained 40 pounds in weight, and has since enjoyed his usual health.

Reëxamination, May 19, 1916, revealed fibrillary twitchings in the legs; otherwise the neurologic examination was negative. His mental condition was entirely normal, and for a year and a half he has held a position of manager and buyer for a large department store.

Epidemic Type

Case 3.—*History.* In January of the present year I saw, in consultation with Dr. Martin Burke, a man, aged fifty years, married, the father of four children. He was a merchant and had led a rather sedentary life. In recent years he had put on considerable weight. There was no history of syphilis. Formerly he had been rather free in the use of alcohol, but of late years he had been quite moderate in this respect.

There was no history of trauma, mental or physical. The disease from which he suffered was of acute onset and was ushered in by excruciating pains in the extremities, beginning in the arms and gradually extending to the trunk and legs. These pains were sharp and shooting in character, requiring analgesics for their relief. They continued with uninterrupted severity for fully a week. On the third day, curious muscle jerks and twitchings made their appearance in the arms and legs, and later in the trunk and abdominal muscles. At first they were quite active in the upper extremities, so that finer voluntary movements were interfered with. On standing and walking, while there was no true ataxia, a slight disturbance of the harmony of movement was manifest, owing to the effect on the extremities of the constant muscle waves and twitchings. There was slight fever from the very beginning, which continued throughout the course of the affection, ranging from 100° to 102° F. The pulse was accelerated, and varied from 100 to 110 beats a minute. Even during the first week a tendency to nocturnal delirium was noted. The patient thought that strange persons were in the room, and became anxious and apprehensive; at other times, he imagined that he was in the country and wanted to get up and go

out for the cows. At first the delirium was only at night, but subsequently evidences of mental confusion were present also during the day, with memory falsifications and hallucinations. He frequently talked as if he had been out of the house a short time before, described what he had seen at the moving picture show, whom he met on the street, and the conversations that he had. Occasionally, he thought he was on the sea, and that his bedroom was a cabin on a ship. He was in a depressed mood much of the time. At other periods he was rather excited and talkative. Later the mental confusion took on the aspect of a mild form of Korsakoff's syndrome, which persisted up to the time of his death.

Examination. January 22, 1920, the patient was large and obese, with a heavy, prominent abdomen. The face was flushed and the eyes bright. He was quite responsive and answered correctly questions as to his symptoms and mode of onset. The gait and station showed no Romberg symptom and no ataxia, but yet were slightly altered by the incessant spontaneous muscle spasms and twitchings. The articulation also presented at times a very slight disturbance, which was to be ascribed to the occasional muscle waves in the musculature of the face and tongue. When the patient was stripped and in a recumbent posture, the muscles of the trunk, abdomen and legs were observed to be in a very active state of myoclonus and myokymia. This condition had been present in the upper extremities, but had subsided and was not present at this examination. An occasional fibrillary twitching or wave was to be noted in the facial musculature and was also present in the tongue muscle, which may account for the very slight dysarthric disturbance that was noted. Coarse muscle waves and fibrillary twitchings were present in all the muscles of the lower extremities, especially on the posterior aspect, in the glutei, hamstring, and calf muscles. At times these movements were so strong as to produce a slight but distinct locomotor effect of the extremity; but as a rule these sudden brief contractions of portions of the muscle mass were not strong or pronounced enough to produce movement or changes in the posture of the extremity. Percussion of the muscles revealed an increased myotatic irritability and a marked accentuation of the idiomuscular response. The most unusual muscular phenomena, however, was to be noted in the abdomen. The prominent abdomen was tossed about in a most bizarre and unusual manner by coarse muscle waves and contractions. I have rarely observed a more striking symptom than that of the abdomen being rocked and contorted by these innumerable waves of muscle contractions. There was no paralysis of any muscle group, but a state of general muscular weakness was present. There was no singultus.

Sensation was normal, and there were no paresthesias, although numbness and tingling were present at the onset of the disease. The pupils were equal, and reacted promptly to light and accommodation. There was no

nystagmus, and the fundus oculi was normal. The cranial nerves were normal.

All of the tendon reflexes of the upper extremities were elicitable and active (the supinator, biceps and triceps jerks). The knee-jerks and Achilles-jerks were also present and equal.

The plantar reflex was normal (no Babinski response). The abdominal reflexes were elicitable and were quite exaggerated. The heart was enlarged and the heart sounds were rather feeble. There were no murmurs. The pulse-rate was 100 beats to the minute. The systolic blood-pressure was 170. The lungs were normal. The urine showed a trace of albumin and a few hyaline casts. There was no sugar. The phenolsulphonephthalein tests disclosed a renal functional activity of 60 per cent.

Subsequent Course. February 3, 1920, the patient's condition was decidedly worse. The temperature ranged from 102° to 103° F.; the pulse was more rapid, the breathing, hurried. The lungs were free from rales, and the heart sounds were weaker. The mental condition was worse. There was nocturnal delirium, with Korsakoff's syndrome. The patient imagined that he went out and had been to the movies earlier in the day; he talked as if he had met me a few hours before, and that he was going out again shortly. He related constantly imaginary events of this kind, with occasional hallucinations, and at times saw strange faces and imaginary people. In other respects he was fairly clear, knew those about him, and knew that he was in his own house; but there also was a tendency for him to become somewhat confused and disconnected in his ideas. The pains had ceased entirely and required no special medication. Muscle twitchings and contractions still persisted and were somewhat less active. The abdominal musculature appeared to be the storm center of the contractions at that time, and gave the patient the greatest discomfort. The hand placed over the calf muscles, however, revealed a sense of undulation which was scarcely visible to the naked eye and was evidently dependent on deep-seated muscle waves and twitchings that were not registered on the surface.

The abdominal reflexes were still quite active and showed a hyper-excitability of the reflex response. The knee-jerks were difficult to elicit, and were diminished. The Achilles-jerks were not obtained. The plantar reflexes were normal.

The patient continued in this condition, gradually growing worse, both mentally and physically. Fever ranged from 102° to 103° F. The delirium and myoclonus multiplex continued up to the last. The heart action gradually failed and the patient succumbed five days later, about four weeks from the time of the onset of the disease.

Case 4.—*History.* A man aged thirty-eight years, a clerk, who came under my observation in January, 1920, whose previous history was negative,

had been a resident of New York for some years. The onset of the disease was sudden, and was ushered in by very severe shooting pains in the feet and legs. These were most distressing in their severity, and continued for about four or five days. After this they diminished somewhat in the lower extremities, but appeared in the hands and arms. He stated that during the first few days the feet and legs were numb from the knees down, but this passed away with the pains and did not return. The pains were described as sharp and biting in character, both in the lower and in the upper extremities. The muscular twitchings were not observed until the sixth day of the disease, when they made their appearance in the lower extremities. They appeared only after the pains had diminished in intensity and were subsiding. Later the muscular twitchings extended to the muscles of the trunk and were especially severe in the region of the abdomen, the muscle walls of the abdomen being the seat of muscular waves and contractions which, although not painful, caused the patient considerable discomfort and uneasiness. The arms were also affected with the muscular twitchings, but in a lesser degree. From the first and during the first two weeks of the disease there was a moderate fever, the temperature not rising above 100° to 101° F. The pulse was somewhat exaggerated, and ranged from 85 to 100. At times during this period there was nocturnal delirium. This was not very severe, but it was stated that the patient would carry on imaginary conversations, and would see strange faces and menacing figures in the room, and was at times apprehensive, restless and excited, attempting to get out of bed and go out in the hall. During the day he was comparatively free from these exciting episodes, but was somewhat confused and at times was irrational and disconnected in his speech, relating imaginary happenings and adventures.

Examination. There was a condition of generalized myoclonus multiplex, affecting the legs and muscles of the back and abdomen and the upper extremities. There was a slight tremor of the outstretched hands, and on standing and walking a very slight uncertainty was produced by muscular waves and twitchings. The twitchings varied in character and degree in different muscles. There were fibrillations, muscle waves, and even contractions of the entire muscles, although the fibrillary and wavelike movements predominated, and it was only occasionally that the entire muscle was observed in momentary contraction. There was but little motor effect produced on the extremities, and the muscle disturbance was of such character as to expend itself in partial muscular contraction without much locomotor effect. The contractile manifestations were generalized, and bore no especial relation to individual muscles or to their synergic activities. They were most marked in the muscles of the calf and posterior aspects of the thigh. If the hand was placed on the calf muscles or the abdominal wall, there was distinct sensation of wavelike movements and undulations,

which was very characteristic. There was no paralysis of any muscles or muscle group, although a state of general muscular weakness was complained of. The muscle and nerve trunks were sensitive during the first week of the disease, and then subsided with the pain, and after this there was no demonstrable tenderness of nerve trunks or muscle tissues. In the early period of the disease there was a marked tendency to sweating, which was still present, but in a lesser degree. On direct percussion of the muscles the myotatic irritation was found to be increased and the idiomuscular response was very pronounced, a large welt developing at the side of the percussion which gradually subsided.

The pupils were equal and responded to light and accommodation. The cranial nerves were normal. The fundus oculi was normal. No myokymic twitchings were noted in the face or tongue. The arm-jerks were present (superinator, biceps and triceps), and were equal on the two sides. The knee-jerks were present and equal. The Achilles-jerks were not elicitable. The plantar reflexes were normal. The abdominal and cremasteric responses were present, with some exaggeration of the abdominal reflex. Pain sensibility of the leg, below the knee, was somewhat blunted; otherwise the sensibility, both superficial and deep, was normal. The heart, lungs and urine were negative.

Case 5.—*History.* A single man, aged twenty-five years, a conductor, suffered from sharp shooting pains in the back and legs which began suddenly. They appeared at first on one side, but a day or two later on the opposite side. These were very severe and caused acute suffering, especially at night. They gradually extended to the trunk and arms, and at the end of a week began to subside. The characteristic muscle twitchings were noted during the end of the first week in the legs, trunks, abdomen and arms in the order mentioned, and appeared to follow in the wake of the pains. The abdominal muscles were especially affected by the spasmodic and undulating, wavelike movements.

There was moderate fever and an acceleration of the pulse, with some tendency to excessive sweating. During the first week of the disease the patient was delirious at night, his thoughts wandered, and he saw strange faces and strange people in the room and talked disconnectedly. At these times he talked as if pursuing his ordinary occupation, calling out the names of his fellow-workers and giving orders. These delirious manifestations subsided at the end of the second week and did not recur.

Examination. The patient was well developed and in good general health. The gait and station were normal, with no weakness or paralysis in the extremities or of any muscle group. He complained, however, of general muscular weakness and of being easily fatigued. There was no tenderness of the nerve trunks or of the muscles. The tendon reflexes of

both upper and lower extremities were elicitable and were equal on the two sides. Percussion of the muscles revealed marked myotatic irritability and a well-marked idiomuscular response. All qualities of sensation were normal. The cranial nerves were normal. The pupils reacted normally, and the fundi oculi were normal. The heart and lungs were negative. The urine was normal. The Wassermann test of the blood was normal.

Cases 6–9 (abstract of case reports).—In February and March, 1920, four case of the epidemic type were seen, in consultation with Dr. Lewis A. Conner and Dr. William R. Williams, in the medical wards of the New York Hospital. These cases presented the same symptoms but in somewhat milder form than those which have just been described. All were in young adults, three of whom were men and one was a woman. The onset was acute, and accompanied by sharp shooting pains in the extremities and trunk which continued from four to five weeks. In all four the myoclonus and myokymia multiplex were limited to the muscles of the trunk and especially the abdominal musculature. It was also present in the muscles of the lumbodorsal region.

There was no well-defined delirium in any of these cases. In all, however, there was present insomnia, great restlessness, apprehension and irritability. There was no tenderness of the nerve trunks and no anesthesias. There were no evidences of weakness or of paralysis in any cranial or spinal distribution.

The knee-jerks were present, and the Achilles-jerks were elicitable in all save one. In this group of cases the pains were more persistent and severe and the muscular jerks and twitchings milder than in those observed in the earlier period of the epidemic. Blood culture was taken in two cases and found negative. There was no leukocytosis. The spinal fluid showed no abnormalities in three cases; in one there was a slight increase of lymphocyte (30) cells. All the patients eventually recovered.

Comment.[1] The cases just described present a striking similarity in the clinical picture, varying only in degree and in severity. The special and distinguishing symptoms are the muscle waves and twitchings, and the shooting pains. Often there is delirium. This was a marked feature of all the cases, except those appearing in the later period of the epidemic when a mild and comparatively localized type of myoclonus multiplex made its appearance.

[1] Cases of the epidemic type have been observed by Boveri, P.: British Med. Jour., April 24, 1920, i, 570. Pardee, I. H.: Arch. Neurol. and Psychiat., July, 1920, iv, 24, and later reports will no doubt show the comparative frequency of this clinical type. So far as I am aware, examples of the sporadic form have not been previously recorded.

The myoclonus and myokymia multiplex, however, are alone characteristic, as pain and delirium may occur in the course of other acute infections.

The disease begins abruptly, with shooting pains, which increase in intensity and rapidly become generalized. These may begin in either the upper or lower extremities. In the cases that I observed they were limited to the trunk and extremities and were not manifested in the sensory distribution of the cranial nerves. In all of the cases they were exceedingly sharp and caused acute suffering. Rarely were paresthesias noted, with occasional blunting of pain sensibility. The muscle jerks and twitchings followed either immediately in the wake of the pains or more commonly after an interval of a few days. Usually they continued long after all pain had disappeared. All degrees of muscle contractions were present, namely, fibrillation (myoclonus multiplex fibrillaris) muscle wave (myokymia) and contractions of the whole body of the muscle (myoclonus). The surface of the body reflected a variety of muscle contraction with only slight, if any, locomotor effect on the extremities. When the myoclonus was of a more severe type, the gait and station and voluntary movements of the arms were slightly disturbed by the play and undulation of the muscles.

In the sporadic cases, the muscle waves and twitchings were generalized, and this was also true of the earlier cases of epidemic type which came under my observation. Later, when the epidemic was on the wane, a milder type was encountered, without active delirium, and muscle twitching was limited to the lower half of the trunk muscles. In this group of cases, pain was quite severe and very persistent. No other evidences of organic disease of the central nervous system were demonstrable. One of the symptoms was the severity of the involvement of the muscles of the abdomen in all of the cases. This is rather significant, as I have not observed it in anything like the same degree in myoclonus and myokymia multiplex from other causes. Singultus was not observed in any case.

Differential Diagnosis.—The nature of the disease becomes clear as soon as the characteristic muscle jerks and twitchings make their appearance. Before this it would be difficult to exclude any acute disease beginning with sharp pains, and presenting the other evidences of a general infection.

Multiple neuritis with delirium may be excluded by the absence of motor or sensory paralysis and of tenderness.

Acute poliomyelitis may also be excluded by the absence of paralyses and consecutive muscular atrophy. Dubini's disease, an obscure affection of the nervous system, which is epidemic in certain parts of Italy, notably Lombardy, may also be excluded. This affection in its more acute form is characterized by headache and backache, and is followed by myoclonic contractions of cerebral origin; hence the term chorea electrica; also convulsive attacks resembling Jacksonian epilepsy. Later there is paralysis of certain muscle groups which had been the seat of myoclonus, with wasting and changes in the electrical reaction. It is an obscure form of encephalomyelitis which may occur in acute and chronic forms. The sensorium is, as a rule, free. So far as I know, the disease has not been observed in this country.

The affection might present a marked resemblance to the infectious chorea with mental symptoms (chorea insaniens). The nature of the motor disorder is, however, quite different. In chorea, there are purposeless, incoördinate movements, with marked and characteristic motor effects in contrast to the muscle jerks and twitchings of the myoclonus-myokymia type, which are not under synergic control, and which are indicated by waves and undulations rather than by movements of the part. In both diseases, infectious chorea and infectious myoclonus, the mental disturbances are those of toxic delirium. In the more severe cases (chorea insaniens), the symptomatology is that of a grave toxic psychosis with chorea. A similar termination may occur in the more severe forms of infectious myoclonus and a myoclonus insaniens may result, in which a grave toxic psychosis is associated with the motor manifestations of myoclonus multiplex.

Epidemic encephalitis, or lethargic encephalitis, should be especially considered in this relation, as it has reached epidemic proportions at the present time and may occur in a variety of clinical forms: cerebral, spinal and neural. What has been described as epidemic myoclonus multiplex undoubtedly belongs to this group, and represents a special "myoclonus-myokymia type" of this affection, a point of view which is strengthened by the coexistence of

undoubted cases of epidemic encephalitis with myoclonus and myokymia multiplex. The relation of the "sporadic type" to the epidemic form is, I believe, still an open question and cannot be settled until we know of the etiologic factors involved.

Conclusion. The acute infectious myoclonus multiplex may, therefore, be regarded as a definite clinical type of acute neural infection.

In its epidemic form, it is a part of the large clinical group that has been so prevalent during the last two years in this country and in Europe—the epidemic of lethargic encephalitis.

The relations of the sporadic to the epidemic type of infectious myoclonus multiplex is still problematic, although it would appear probable that they are of similar origin, and that the epidemic encephalitis has been appearing for a considerable time unrecognized, in certain sporadic forms. That the disorder is of infectious origin and referable to a microörganism or its toxic product is made clear by the mode of onset, course and general symptomatology.

As to special etiologic considerations, it would appear likely that a special strain of the organism has acquired an affinity for certain tissues of the nervous system, and in this way the peculiar and very limited clinical reaction of infectious myoclonus multiplex has been produced. Other factors of a more theoretical nature may also be considered, as exhaustion or biologic inferiority of certain neural systems which render them more susceptible to the deleterious influences of disease.

To those who are interested in the theory of the elective localization of bacteria, the organisms or virus obtained from cases of this clinical type, with its peculiarly limited form of neural involvement, would offer especial advantages for experimental study.

EVENTRATION OF THE DIAPHRAGM WITH REPORT OF A CASE [1]

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Among the rare lesions of the diaphragm is the condition originally described by Petit in 1790 and termed by him eventration. This term, though generally used, is a misnomer because no abnormal opening of the diaphragm exists. Such an opening constitutes a hernia diaphragmatica vera when the projecting abdominal viscera are covered with peritoneum, or a hernia diaphragmatica spuria when no peritoneal covering exists. In eventration there is simply a thinning or relaxation of the diaphragm, the layers remaining intact and the structure assuming an elevated or higher position than normal. Isolated writers have preferred such terms as these: "high position," "elevation," "dilatation," "relaxation" and "congenital insufficiency." Bayne-Jones, in 1916, collected the reported cases to that time and reported one of his own, making 45 in all. Since that time we have been able to find reports of 2 more. These cases with the one we report make a total of 48 cases on record at the present writing.

With regard to the etiology the weight of evidence would seem to favor a congenital origin. Some of the arguments advanced are: (1) Its occurrence in the fetus and the newborn; (2) its association with other congenital anomalies; (3) the involvement of

[1] From the Departments of Medicine and Roentgenology of the Jefferson Medical College and Hospital. Presented in abstract before the Association of American Physicians, Atlantic City, May 4, 1920.

the left side in almost all cases—which coincides with the complexity of the development of the left diaphragm; and (4) the absence of compression of the lung and contiguous structures.

Considered as an acquired lesion it has been supposed to follow disease of the muscle or of the nerves and as a result of greatly increased abdominal pressure. Among the latter conditions pregnancy, ascites, megalocolon are important in producing increased pressure. However, as Bayne-Jones points out, "If this factor of increased pressure in the abdomen bore an important etiological relationship to eventration, the frequency of pregnancy in general—and oftentimes in the same individual—should find a counterpart in a large number of women suffering from eventration of the diaphragm." As a matter of fact the lesion is uncommon in women. Among 45 collected cases there were 36 males and 9 females.

The high position of the diaphragm due to the contraction of pulmonary fibrosis and adhesive pleuritis is a different lesion from that under consideration and will be discussed under diagnosis.

The clinical notes of our case are briefly as follows:

E. N., white, female, married, aged thirty-nine years, was admitted to the Jefferson Hospital on December 4, 1919, complaining of pain in the epigastrium and in the back with attacks of vomiting. Family history negative. Past personal history negative except for the usual diseases of childhood. She states that she has always been in good health until the present trouble. No pregnancies.

History of Present Illness. In September, 1919, that is about three months prior to coming under observation, she began to have pain in the epigastrium and left lower chest associated with attacks of vomiting. The pain radiated to the back. The pains have continued with varying intensity until the present time. At times they seem to bear some relation to the taking of food but the relationship is not constant. Shortly after the onset the patient noticed that she became easily short of breath on exertion and was losing weight. The physician who saw her at the beginning of her illness made a diagnosis of gastric neurosis and an *x*-ray at that time aided in the elimination of gastric ulcer or cancer. Physical examination revealed the following: A fairly well nourished adult female, no jaundice, eyes, mouth, ears and neck normal. Chest well formed and symmetrical, expansion definitely limited on the left side, especially over the lower portion. Apex beat not visible or palpable. Percussion revealed

tympany below the third rib in the anterior axillary line merging with the tympany over stomach below. Posteriorly on the same side the percussion note below middle of scapula was high pitched and resembled the so-called flat tympany. The percussion note of the rest of the chest was clear and resonant. Breath sounds were everywhere normal except over the area of altered percussion note on the left lower chest where they were practically absent. During the auscultation of this area a sound suggesting a splash was heard when the patient was moved. No coin sound could be elicited. The physical signs elicited suggested the possibility of a hydropneumothorax and this was our provisional diagnosis when the patient was admitted to the hospital. The blood examination revealed the following: Hemoglobin, 88 per cent.; red blood cells, 4,700,000; white blood cells, 9600; differential white cell count: large mononuclears, 8 per cent.; small mononuclears, 19 per cent.; polynuclears, 69 per cent.; eosinophils, 4 per cent. The urine examinations were repeatedly negative. A paracentesis of left chest in sixth interspace in midaxillary line was negative.

The fluoroscopic and stereoscopic *x*-ray examination revealed the following: The left diaphragm was found considerably higher than the right and does not move on forced inspiration. The dome shape is retained and no adhesions are evident at the costophrenic angle. The diaphragm has the appearance of an eventration, the cause of which is not apparent. There is just a suggestion of a slight amount of infiltration at the left apex. The barium meal in stomach shows the cardiac end of the stomach in its proper relation to the left diaphragm, but because of the enormous distention of the colon with gas we are unable to determine whether the stomach is normal or not. We believe that the position of the diaphragm is not due to the gas in the colon.

As we were preparing this paper for presentation before the Association we came across another case of high position of the diaphragm in a baby only a few days old who was referred for *x*-ray examination for a fractured arm. The left diaphragm was at the level of the second interspace. The heart was not displaced. There was no question of any abdominal trouble and there were no symptoms of any kind suggesting either trouble above or below the diaphragm. This case would seem to emphasize the congenital origin.

Discussion. In the past most of the diagnoses were made at postmortem or operation. The symptomatology and physical examination suggested a variety of lesions. In one group the

symptoms were referable to the chest and pneumothorax, pneumohydrothorax, pulmonary fibrosis, chronic adhesive pleuritis with elevation of the diaphragm, etc., were diagnosed. In another group gastro-intestinal symptoms predominated and the patient was considered as having a gastric lesion, a diaphragmatic hernia, etc. With the advent of the *x*-ray many of the difficulties in the differential diagnosis of these lesions were cleared up. The case of Sailer and Rhein[1] illustrates well this point. Their patient was considered as having at various times either a pneumothorax, diaphragmatic hernia, pulmonary cavity or an elevated diaphragm. The *x*-ray was taken immediately after death and not developed until after autopsy, but the study of the plates showed that the diagnosis could have been readily made by this method.

The *x*-ray made the diagnosis in our case. In a number of physical examinations made after the *x*-ray had established the diagnosis I came to the conclusion that I would have been put on the right track if I had paid more attention to the inspection and palpation of the costal margin movements as pointed out in recent years by Hoover. There was a distinct widening of the subcostal angle on inspiration. The widening seemed to be due principally to a divergence of the left costal border. Several physicians who saw the patient with me at different times were able to verify this observation. The high position of the diaphragm placed it at a mechanical disadvantage in its function as an antagonist to the intercostal muscles. Low position of the diaphragm occurs in many of the conditions confused with eventration, such as pneumothorax, hydropneumothorax, etc., and as a result of which narrowing of the subcostal angle occurs. In certain forms of obsolete pleurisy with adhesions to the diaphragm and the chest wall and the diaphragm and lung there is likewise narrowing, according to Hoover, because under these conditions it has acquired a mechanical advantage in its traction to the costal border by reason of the adhesions which, acting as points of fixation, give approximately a straight line to the phrenic muscular strands from the central tendon to the left sternocostal region.

[1] American Journal of the Medical Sciences, 1905, cxxix, 688.

Among the reported cases the left half of the diaphragm is noted as being involved in all 46 instances excepting 3. The dome is usually regular in outline in contradistinction to that which is seen in the elevated diaphragm of adhesive pleuritis. As the structure is thinned its outline on the fluoroscopic screen is less distinct than the normal diaphragm shadow. The lung on the affected side is often hypoplastic. The heart is oftentimes normally placed, although it may be found displaced in either direction in involvement of the same half of the diaphragm.

One of the arguments adduced in favor of the congenital origin of this lesion as against an acquired elevation due to the traction of adhesions is the external symmetry which the chest presents on inspection. This is in striking agreement with the observations which Ellis[1] noted in his report of a case of congenital absence of the lung. This same writer collected 18 instances of what appeared to be certain examples of the condition. In all of them the chest was externally symmetrical, the opposite lung, heart, fluid or abdominal organs taking the place of the missing organ. If this is true in pulmonary aplasia it is likewise true in eventration with pulmonary hypoplasia and is one of the strongest arguments against an acquired origin of the disease. In acquired lesions elevating the diaphragm to the extent seen in congenital eventration there is obvious flattening of the chest wall. The lung is the seat of obvious and demonstrable disease and the *x*-ray shows many and dense shadows. The lung above the diaphragm in eventration is normal unless there be some intercurrent pulmonary disease, such as pneumonia, which, however, has no etiological relationship to the diaphragmatic condition. The inspection of the chest reveals nothing of note as far as symmetry is concerned. In cases of eventration associated with aplasia of the lung in the affected side the opposite lung may be enlarged sufficiently to extend over and furnish sufficient pulmonary tissue to give physical signs on the side of the absent organ. Even in hypoplasia the opposite lung may extend over to the hypoplastic side. Clinically it is not possible to demonstrate such overlapping. Even with the *x*-ray

[1] American Journal of the Medical Sciences, 1917, clvi, 33.

considerable difficulty may be encountered unless the shadows of the bronchial tree are clear and suggest a different distribution than normal.

DISCUSSION

Dr. J. Ramsay Hunt, of New York, said that one should take into consideration that these structural changes were associated with striated muscle fiber. The diaphragm was innervated by the sympathetic system. If the nerve was cut, paralysis was produced but there was preservation of tonus; if the splanchic were cut, tonus was lost but movement was preserved.

Dr. C. F. Hoover, Cleveland, Ohio, said that the observation of increased movement of the costal margin on the affected side would be of service in the differentiation between hernia and eventration. In hernia there was a large portion of the stomach in the thorax and the movement of the costal margin was not modified. One could stuff any quantity of viscera in the diaphragm but the movements of the costal margin were not changed. There might be dulness in the left thorax due to the retraction of the lung. In the other case there would not be elevation pitch of the percussion sounds.

Dr. S. J. Meltzer, of New York, asked if the Litten phenomenon were observed. That would give information as to where the diaphragm was.

Dr. Elmer H. Funk, of Philadelphia (closing), said that pathological studies were made on 20 reported cases, but in none of these had any intensive work been done on the innervation. He could pay a tribute to the value of the work of Dr. Hoover on the diaphragm. He was impressed with the necessity of investigating the movements of the costal margin. The Litten phenomenon was absent in this patient.

EXPERIMENTAL STUDIES IN RADIOTHERAPY

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The past five years have witnessed an extraordinary development of interest in the results of the radiation treatment of malignant tumors. The extravagant claims which were originally made for radium are now being repeated for *x*-ray, especially by the German clinicians. Opposed to this optimism there is a widely expressed doubt, chiefly on the part of the surgeons, as to the ultimate benefits of radiation of malignant tumors. Unquestionably there is a middle point upon which agreement will some day be reached, but it is evident that the final decision on the claims of those who favor radiation treatment must await the ultimate survey of the material after the expiration of the time which is now required for surgical reports of cures of malignant neoplasms. That is, at least five years must elapse before there is any certainty that the tumor will not return. Unfortunately both the surgeon and the radiotherapeutist seem not to recognize the fact that recurrences may take place even after a period of five years, though only in an exceedingly small proportion of cases. The writer has seen recurrences follow operations for carcinoma of the breast after periods ranging from nine to thirteen years, and there are many similar instances in the literature of the subject. Then, too, the radiotherapeutist must publish not only his cures but also his failures, as the surgeon has done, so that some comparison can be drawn as regards the relative success of operative treatment and radiation. This but few have been willing to do so far.

All these questions concern only tumors which have a tendency to metastasize. It has long been recognized that some of the more

benign types of epithelioma of the face yield to both *x*-ray and radium in approximately 90 per cent. of instances, unless the tumor has involved bone or cartilage, in which case it becomes, as is well known, much more resistant to any radiation. It is generally held at the present time that these relatively benign tumors may be properly treated with *x*-ray or radium if they are not too extensive and if it is understood that surgery will be promptly used when the radiation effects are not favorable. This is the type which the dermatologist has in many instances cured with caustics, freezing with carbon dioxide gas or other similar means. The caustics and the freezing, however, are gradually being abandoned, since if the tumors do recur the scarring is considerable and interferes with other types of treatment. Radiation is much better.

It is therefore the malignant metastasizing tumors which are the subject for immediate discussion, and of these only those which are operable are regarded by the surgeon as promising. The inoperable forms should, of course, be treated in any way which permits the slightest hope of cure or even of palliation, and this is now generally acknowledged by everyone to be the field for radiotherapeutics, the question as to whether radium or *x*-ray is the most efficient being still the subject for much discussion. Even the most enthusiastic believers in radiation are now admitting, with some reluctance, that it is often impossible to treat effectively certain types of tumors; for example, osteosarcomata; chondrosarcomata, the malignant form of chondroma; gliomata of the brain; mediastinal and peritoneal carcinomata and some other malignant tumors of the internal organs. On the other hand, lymphosarcoma is being acknowledged at the present time to be out of the province of the surgeon, as the tumor is almost always multiple and may diffusely involve the lymphoid structures of the body, though effective palliation is obtained by radiation. Carcinoma of the uterus also is an especially favorable condition for radiation, as this tumor is so often inoperable even when not very extensive and seems in many instances to yield, with unusual rapidity, to moderate doses of radiation. Even though recurrence takes place the patient's life has probably been prolonged, and often in great comfort.

It has been not infrequently stated as an advantage of radiation

methods in contrast to surgery that the process is "painless," that "the agent destroys the disease at a greater distance than the knife can reach," and that the remedy is attended "with no unpleasant consequences." This is, however, far from true. The amount of radiation required to affect a malignant tumor is so large that not only the tumor tissue but also the surrounding healthy tissue is frequently seriously damaged, and those who have had an opportunity to observe some of the numerous recto-vesical-vaginal fistulæ which have been produced by enthusiastic users of radium would hardly judge from the patient's expressions on the subject that the results were without inconvenience. Refuge cannot be taken behind the fact that occasionally spontaneous fistulæ occur because of extension of the growth, since they are unquestionably much more frequent following radiation. So, too, the dangers of stimulation of tumor tissues at a distance, more and more acknowledged by those who are using rays in treatment, are unquestionable and the death of the patient may be accelerated when there is extensive involvement at a distance from the point of application of the radiation. Again, the large quantities of radiation which must be employed in order to produce an effect on the tumor often incite serious general reactions so that the patients frequently suffer from nausea, headache and febrile phenomena extending over periods of a week or ten days following a single treatment; and the more courageous of the radiologists are now acknowledging the fact that occasionally the death of the patient follows a large dose of either radium or *x*-ray. This is, indeed, no criticism of the method, for surgery itself acknowledges a large mortality, and that there should be a radiation mortality is not astonishing considering the amounts of energy which are set free in the body during the application of massive doses of radium or *x*-ray. It must be remembered that cancer is a fatal disease and some risks may properly be assumed in attempting a cure. The time is evidently coming when the question will be one not of mortality or of discomfort but simply of whether surgery can relieve the condition as efficiently as radiation. When that question is answered, and it may be in the next ten years, a very interesting phase of medicine will have passed from the realm of assumption to that of fact.

There are many still unsettled problems concerning both methods of radiation treatment. The questions of filtration, of dosage, of wave length, of time factors are still in flux. It has never been shown, for example, that the extremely short wave lengths which are produced by radium or mesothorium are more effective in killing the cells of malignant tumors than are the longer wave lengths at present produced by the commercial *x*-ray apparatus. It is not settled whether or not mesothorium is more or less effective than radium, though the efforts of the rival commercial producers of these two agents to run down each other's products (appearing chiefly in the daily press) are not without their humorous aspects, especially as the fact seems to be generally forgotten that mesothorium, as ordinarily produced, contains a considerable amount of radium, often as much as 25 per cent.

The fact is not yet determined whether or not long wave lengths or short wave lengths of the roentgen rays are the more effective in destroying tissue. The physicist, even if he is biologically trained, cannot see why the question is anything but a matter of energy set free in the cells which it is desired to treat and that the wave length factor is of importance solely from the point of view of penetration, the short wave lengths penetrating the tissues more effectively than the long. It has been argued as an analogy—and analogies are always dangerous logically—that because the ultraviolet rays from a mercury arc lamp will burn the skin in a few minutes and the long heat waves from a steam radiator will not, that therefore the short rays of radium should be more effective than the longer rays of the *x*-ray tube. But the physicist immediately recalls that the long heat waves and the longer light waves penetrate the tissues without giving up much of their energy, such penetration being easily demonstrated by the possibility of obtaining the spectrum of sulphemoglobin in a patient's blood by holding his hand in the beam of light from a powerful electric arc and examining through the tissues with a spectroscope. Evidently such rays pass through 1 cm. of tissue without much loss. On the other hand, all the ultraviolet light is absorbed in the first millimeter or so and therefore gives up all of its energy in this region. It is commonly said, also, that radium is much more effective in the therapeusis of myelogenous

leukemia than is *x*-ray, but this is by no means certain. Most of the *x*-ray that has been used in the treatment of leukemia is that produced by a tube running at a voltage of not over 85,000 volts and filtered through 3 mm. of aluminum. Such rays fall to one-half value in about 10 cm. of tissue. Beyond this point the quantity introduced is so little that it may very well stimulate. If higher filtration is used, such as 0.5 mm. of copper or zinc, 75 per cent. of the rays penetrate 10 cm. and much better results are obtained, especially if the tube is run at 100,000 volts, which brings out very strongly the characteristic or fluorescent rays of the tungsten anticathode. Under these conditions much more of the energy is concentrated in the shorter wave lengths. For example, with 85 kilovolts and 3 mm. of aluminum the half-wave length in aluminum is some 6 mm., while with the higher voltage and denser filter it is about 21 mm. On the other hand, small quantities of radium, say 20 mgm., filtered through 2 mm. of lead, will cause a rise of leukocytes if applied on a leukemic spleen even for a number of days, stimulation being the result rather than destruction.

The same question applies to the treatment of tumors, and even less is known of the effects, because there is no convenient index to measure the results as there is in leukemia, in which a blood count taken a few days after radiation gives a pretty good estimation of the destructive action of the *x*-rays.

Again, the measurements of dosage are extremely crude from a physicist's point of view; the erythema dose as determined by the patient's skin fluctuates with the filtration, probably exceeding 20 per cent. The pastilles and photographic paper ordinarily used for determining the effects of *x*-ray also give very inexact results, and neither of these methods can be used with radium with any convenience; so the whole question needs thorough revision, with accurate apparatus and the application of strictly controlled experimental tests, using animal tumors as the material for application of the ray.

Then, too, the term "milligram hours of radium" is as inaccurate as the term "milliampère minutes of *x*-ray." Unless the filtration and distance are known no definite conclusions can be drawn. Ultimately it will be necessary, as has been repeatedly suggested,

to standardize the *x*-rays in terms of radium constants, and the only way in which this can be done is by the use of ionization methods so fertilely applied to the investigation of the theoretical side of both types of radiation.

Practically, of course, no one would ever use an *x*-ray tube in therapeutics if unlimited quantities of radium were available. The latter has been aptly termed a pocket *x*-ray tube. Its convenient size, its portability and the constancy of its radiation factors make it a substance especially useful in this form of therapeutics. But, unfortunately, the quantity of radium is limited and probably always will be. This means an enormous capital charge which makes the cost of radium therapy high and places it quite beyond the use of a large proportion of the population. When it is remembered that each year 90,000 people in the United States die of cancer and that the total available quantity of radium is probably not more than 200 grams, the small proportion of people that can be treated is obvious. *X*-ray is cheaper and the only question is whether or not it is as effective. Theoretically it is perfectly possible to produce *x*-rays of approximately the same wave length as radium, but the difficulties and dangers of handling apparatus of the high voltages required (some 300,000 volts) and the impossibility at the present time of obtaining *x*-ray tubes which will stand these voltages, have so far kept back the replacement of radium by *x*-ray. The future development by electric engineers of apparatus and tubes may obliterate the differences.

Tonight I want to show you some slides which illustrate certain phases of the experimental approach to a solution of a few of these problems. Some years ago Dr. Prime and I determined on mouse tumors the lethal dose of radium, the amount and distance being accurately measured and allowance being made for the fact that radium as used is not a point source and is not therefore subject to the usual rule of the inverse square law. Some phases of this work have since been extended by Bovie. This investigation showed that very large quantities of radium are necessary to kill all the cells of a malignant tumor. Unless all the cells of such a tumor can be killed no permanent cure can be expected, only palliation. The dose is so large that it is evident that the highly resistant tumors

cannot be destroyed by any available quantity of radium, and this, as has been stated above, is now acknowledged in the case of certain types of sarcoma and is probably equally true of many forms of internal carcinoma. Even if it were possible to destroy the cells by suitable doses the body would not survive the radiation. To produce the desired effect the exposure must be given in a single dose, otherwise the amount must be increased, as during the period elapsing between two successive doses the cells are enabled to restore themselves to a certain extent by the washing out of the toxic or destructive products produced in the tissues by the ionization set up by the rays. We showed also that within certain limits one-fourth of the dose given in four times the time was equally effective. Here, again, the limitations of the procedure are rather sharp. The amount of *x*-ray required to destroy an internal tumor with the present commercial machines may mean an exposure of five or six hours. This is the limit of endurance of the human body, though some of the German investigators report that they have been able by the administration of morphin to keep patients fastened to the *x*-ray table and quiet for such a length of time. It is, however, manifestly impossible to keep a patient under an *x*-ray tube for twenty-four hours. The rays must, therefore, be given at a certain rate and must not fall below a limit which is fairly sharply fixed, otherwise the cells will regenerate at the same rate as they are damaged. This condition is demonstrable in leukemic patients by the use of small doses of radium as stated above. The question of effectiveness of soft or hard rays, or, what is more accurate, of rays of longer or shorter wave length, is not yet settled. The difficulty lies in determining the effective energy of the rays. Such determinations have to be made with an ionization chamber which contains no metal and is made of horn, as has been suggested by Krönig and Friedrich, or of celluloid with terminals made of graphite. The most convenient way to do this is to dissolve celluloid in a suitable solvent, mix it with graphite and pour sheets of the mixture and allow them to dry. Such sheets have a relatively low resistance and can be mounted in a celluloid cylinder and connected with a sensitive D'Arsonval galvanometer. The air in the ionization chamber must have the same relative absorption as the thick-

ness of the tissue which is to be exposed; that is, if 1 mm. of tissue is used the air column must be at least 800 mm. in length, as the absorption of such a column of air is equivalent to that of 1 mm. of tissues. Such a bulky ionization chamber cannot be used practically but only to calibrate smaller ionization chambers, which can be inserted under the patient or in the rectum or the vagina to measure the actual quantity of *x*-ray arriving at the point at which the ionization chamber is situated. Only in this way can we determine in any satisfactory fashion the amount of *x*-ray reaching the tumor which is being treated. All other methods are utterly unscientific. No one thinks of guessing at the amount of morphin which is to be given hypodermically to a patient, nor should he guess at the amount of *x*-ray or radium to be applied. Until refined means of measurement can be practically employed, and they are particularly difficult with radium because of the small amount of energy which that substance gives off, treatment by radiation will not be on a scientific basis, and comparison between the two types of rays will not be possible. Unfortunately no commercial apparatus which permits such determinations is on the market. Our own experiments on animal tumors seem to show that soft *x*-rays are more effective than the harder rays produced by filtration through the heavy metals. This has been confirmed by some experimenters and denied by others. Krönig and Friedrich, for example, believe there is no difference between the effects, but their methods of measurement leave much to be desired, and they used an index material—frogs' eggs—which cannot be regarded as comparable to mammalian tissues. The question, therefore, must be regarded as still unsettled.

As an illustration of some of the confusion which exists there will be found numerous statements in recent literature as to the proper filtration for *x*-rays and radium. Some writers have, for example, recommended zinc for *x*-ray filtration as possessing certain peculiar properties which make it preferable to other metals, notably aluminum. Nevertheless, careful measurements will show that equivalent thicknesses of zinc and aluminum pass rays of the same composition. It is true that zinc and copper are less bulky than the equivalent 13 or 14 mm. of aluminum, but the matter is one of convenience only and not of some magic separation of desirable and

undesirable radiations. The *x*-ray tube as at present used gives off a continuous spectrum whose extent is solely dependent on the voltage of the tube, the higher the voltage the more short wave lengths being produced. When filters of substances of an atomic number not higher than about 30 are used, equivalent thicknesses remove equivalent amounts of the longer wave lengths. When substances whose atomic number is just below that of tungsten are employed some rays of shorter wave length are removed and also most of those of longer wave length, so that an approximately monochromatic wave length of 0.2 Ångströms is produced. The amount which passes such a filter is so small that it cannot be used in therapeutics at present. The only way to increase it is by raising the voltage to a much higher figure, which, as has been stated, cannot be done successfully except with experimental apparatus, owing to the breaking down of the tubes and the great spark distance of the high voltage currents. At 100,000 volts 1 mm. of copper is equivalent to 20 mm. of aluminum and 80 cm. of water, only one-tenth of the total energy of the *x*-rays at the wave length stated escaping through such a filter. To obtain a wave length of 0.07 Ångströms, which is that given by radium C, a voltage of over 300,000 would be necessary and the yield even at that pressure would be exceedingly small. To obtain a satisfactory output a uranium anticathode would have to be used, which is not at present possible. This shows some of the practical difficulties which must be overcome before *x*-ray can produce rays approaching those of radium.

For radium, gold, silver, platinum, lead and brass are all recommended as filter substances by different workers.

Other statements showing a lack of knowledge of physics have been made by radiotherapeutists, such as that in using filters the intensity of the radiation is not inversely as the square of the distance. This is, of course, not generally true. The filter itself acts as a source of radiant energy, part of the *x*-ray being scattered, thus somewhat increasing the amount reaching the tissues underneath the filter; but the amount of scattering depends upon the nature of the filter, its diameter, the conditions of running the tube, which gives off *x*-rays not only from the point of impact of the cathode rays against the tungsten anticathode but also from the other

metallic portions of the tube and even from the glass, so that confusing results have been obtained with the ordinary medical methods of measurement by pastilles. When the ionization chamber was employed it was found, as the lantern slide shows, that for all practical purposes the law of inverse squares is followed, the amount of radiation being reduced to one-fourth when the distance is doubled.

Another investigation still under way and promising to be of interest is an attempt to combine the effects of two types of physical agents upon the cells. A definite limit, the erythema dose, is placed upon the amount of *x*-ray which can be passed through a given area of skin, and when this has been done the deeper tissues can still be heated by diathermic applications of electric currents through a neighboring area not sensitized by the rays. The evaluation of this possibility depends upon the accurate determination of the time and temperature coefficient of animal tumors. This is surrounded experimentally with considerable difficulties, but the technic is now sufficiently mastered to make it possible to show that low degrees of heat, such as 41°, 42° and 43° C., at given periods, possess considerable killing power on tumor cells. It does not take quite half a lethal dose of *x*-ray and half a lethal dose of heat to kill the cells; hence, from an experimental point of view, something has been gained. The practical application involves many technical difficulties which will have to be worked out in time, but the results so far suggest the hope that in suitable cases it will be possible to combine the effects of the two agents. The use of these low degrees of heat must not be confused with the employment of the cautery nor with the killing of the tissues by Percy's method, in which the temperature used is much higher than those we have employed.

An interesting by-product of this thermal death-point work was the simple demonstration of the reason why mouse tumors will not grow in the spleen of the domestic fowl. Danchakoff has recently published some interesting observations on the destruction of tumor cells when adult chicken spleen is mixed with certain mouse tumors and implanted upon the membranes of the unhatched chick. She regards the phagocytosis of the tumor cells which occurs as

possibly having an important bearing on the immunity problem in general. When mouse tissues are inoculated into the rat they grow for a period of two to four weeks and then disappear, but are not phagocyted; when, however, they are inoculated into the fowl no growth occurs; hence the conclusion might easily be drawn that some antibody or humoral process destroyed the implants. The explanation is, however, much more simple. The normal temperature of the common fowl is 42° to 44° C., and at the latter temperature mouse tumors are killed in six hours.

In conclusion, it may be said that opportunity has been vouchsafed to touch upon only a few of the many problems which must be solved before the radiation therapeutics of cancer can be placed on a scientific basis, but in this subject above all others in medicine is the wise phrase of Bacon applicable, "The counsels to which Time hath not been called, Time will not ratify."

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PAROXYSMAL TACHYCARDIA OF VENTRICULAR ORIGIN AND ITS RELATION TO CORONARY THROMBOSIS

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THE experimental study of Lewis, Smith and that done in our laboratory are sufficient evidence that interference with the coronary circulation may produce ventricular paroxysmal tachycardia.

The criteria used in establishing the diagnosis of paroxysmal tachycardia of ventricular origin are the following electrocardiographic findings:—A succession of auricular complexes occurring independently of, and at a slower rate than the complexes of ventricular origin; ectopic ventricular complexes at a rate of 150 or more per minute; evidence against possible disturbance in intraventricular conduction (as, for example, bundle branch block); absence of such disturbances in records made between paroxysms; isolated ectopic ventricular complexes resembling in form those of the paroxysm, occurring before or after a paroxysm; and the character of electrocardiograms of the beginning or the end of an attack.

In reviewing the sixteen published cases of ventricular paroxysmal tachycardia that have had accompanying electrocardiograms we have accepted only six as undoubted cases, after the data which we have described are applied in their diagnosis. These are the two cases published by Lewis and one each published by Hart, Butterfield and Hunt, Willius and Vaughan. All of these but one were middle-aged men. The autopsy on one case showed a myocardial lesion which is of the type often following a lesion of the coronary arteries, although the condition of the coronary arteries was not

described. The autopsy on another, a suicide, showed atheromata of the coronary arteries.

Six other cases, three by Hume, one each by Vaughan, Cohn and Fraser and Willius appear to be probable cases. Of the other four cases of Willius, one is questionable and the other three are probably not cases of ventricular paroxysmal tachycardia.

We observed four cases which we consider undoubted examples of paroxysmal tachycardia of ventricular origin.

Case I.—Hospital number 14496: A man, aged fifty-three years, had had syphilis eight years previously. He had received treatment with mercury for three years until he had repeatedly negative Wassermann reactions. Two weeks before admission to the hospital he applied to the out-patient department on account of shortness of breath on exertion, which he had had for two years, and for a feeling of oppression across the upper chest which has been present for three or four months. At this time his systolic blood-pressure was 165 mm. Hg. The urine contained a trace of albumin and many granular and cellular casts.

At 2 A.M. of the night of his admission to the hospital he was awakened by a severe pain in the upper chest followed by a cough with bloody frothy sputum and a persistent precordial pain. He was admitted to the hospital at 4 A.M., at which time he appeared *in extremis*. There was definite orthopnea, his respiration being forty per minute and accompanied by grunting or groaning. He had conspicuous cyanosis of his lips and hands, an ashy pallor of the face and a moist, cool, "clammy" skin. The pulse was small, rapid, weak and "thready," with a rate of 190 per minute. The systolic blood-pressure was 115 mm. Hg and the diastolic pressure was 90 mm. Hg. The outline of cardiac dulness extended 5 cm. to the right and 14 cm. to the left of the midsternal line. No murmurs were heard, but the heart sounds were weak and embryocardiac. Bubbling rales were present throughout the chest.

Electrocardiograms taken soon after admission showed ventricular paroxysmal tachycardia. About ten hours after admission the heart-rate was found to have become 120 per minute. Electrocardiograms taken during the slow rate demonstrated very small narrow ventricular complexes. The heart-rate rose again to 190 per minute about twenty-four hours after admission and the patient died two hours later.

At the autopsy the heart had an unusual shape. There was a definite forward bulge of dull grayish colored muscle in the lower part of the left ventricular wall. This part of the myocardium was that supplied by the anterior decending branch of the left coronary artery. This vessel was found to be completely occluded by a fresh thrombus commencing at a

point 1.5 cm. from the origin of the vessel and extending 2 cm. along the lumen. The wall of the vessel was much thickened and a typical syphilitic lesion was present. The circumflex branch of the left coronary artery showed thickening of its walls and a reduction of the lumen to a diameter of 1 mm. The area of the heart wall supplied by this artery was atrophic and showed an extensive overgrowth of connective tissue.

Case II.—Hospital No. 1875. A salesman, aged fifty-eight years, was admitted to the hospital on December 12, 1915, with dyspnea, pain in the chest and tachycardia. Ten years previously he had been told that he had chronic nephritis and had discontinued the use of protein food and alcohol which had been used previously, at times to excess. There was no definite evidence of syphilis.

His illness began two weeks previous to admission to the hospital, with a sudden pain in the region of the heart while walking. It was sharp, severe and radiated down the left arm and was accompanied by a sense of constriction about the chest and difficulty in breathing. In the first attack he "stumbled home alone" and was given morphin, which relieved him temporarily, but the pain returned and persisted. His breathing was said to have been continuously labored, and cyanosis was observed. He had several attacks before admission, in which the pain in the chest became excruciating, the skin became cold and moist, and the pulse rapid, weak and thready. Rusty blood-tinged sputum appeared and his temperature rose to 101.6° F. Three days before admission to the hospital the patient went into "collapse" and the pulse became very rapid on the day before admission.

On physical examination at the time of admission the patient was stuporous, very cyanotic and dyspneic. The heart-rate was between 180 and 200, the rhythm regular. The outline of cardiac dulness extended 4.5 cm. to the right and 13 cm. to the left of the midsternal line. The heart sounds were clear, with an accentuation of what seemed to be the first heart sound. At the apex region the sounds were weak and rapid.

Moist rales were heard at both bases posteriorly but otherwise the lungs were clear. The liver dulness extended 9 cm. below the costal margin and the abdomen was slightly distended. The systolic blood-pressure was 138 mm. Hg at the time of admission, but fell gradually until it reached 95 mm. Hg thirty-six hours later. Cheyne-Stokes breathing was noted the day after admission.

Pressure over the vagi and ocular pressure failed to produce any effect on the heart-rate. Atropin sulphate (gr. $\frac{1}{75}$ hypodermically) produced no change in the rapid ventricular rate.

The heart-rate was continuously rapid until eleven days after the onset of the tachycardia. The rate ranged from 185 to 248 beats per minute. No cause for the change in rate was ascertained. During the first week of

this period the patient improved distinctly. He became rational, his pain practically disappeared, his lungs became free from rales and he said he was fairly comfortable. The phenolsulphonephthalein output diminished during the period of tachycardia. On the tenth day alternation of the pulse was observed and the heart-rate slowed to 180 per minute. On the eleventh day the heart-rate fell to 120 per minute, while the systolic blood-pressure, which had been varying from 110 to 95 mm. Hg, rose to 154 mm. Hg, while the diastolic pressure was 90 mm. Hg. During the period of relatively slow heart-rate, the patient was worse, being weak, fatigued, and uncomfortable. On the sixteenth day the heart-rate again rose to 190 per minute while the systolic blood-pressure fell to 105 mm. Hg, with a diastolic pressure of 95 mm. Hg. The patient seemed better than during the slower heart-rate, but no increase in the urine output occurred, and he soon began to have increasing weakness. On the twenty-third day he became unconscious and apparently moribund, and died on the twenty-fourth day, eight days after the reappearance of the tachycardia. The heart-rate again slowed to 120 beats per minute a few hours before death, and then gradually became slower until he died. An autopsy was not permitted.

Electrocardiograms showed ventricular paroxysmal tachycardia at the high rate and very small narrow ventricular complexes at the slow rate.

Case III.—Hospital number 1601: A housewife, aged fifty-three years, was admitted to the hospital on October 29, 1915, complaining of indigestion, heart trouble and pain in the throat and arms. Her general health had always been good. There was no history of a severe infectious disease, or of the use of alcohol or of excessive physical or emotional strain. Although married she had never become pregnant, the cause of sterility being unknown.

In March, 1912, the patient began to have weakness and abdominal distress, while in the spring of 1913 she had on exertion an aching or burning in the throat which radiated down the arms, especially the left arm. She said she had an "all-gone, generally depressed feeling," and difficulty in climbing stairs. In December, 1914, the patient had attacks of severe pain in the left side of the chest, which lasted from twenty to thirty-six hours. She was told she had pleurisy, but this pain did not recur. In March, 1915, the patient became very "nervous" and was told she had hysteria. On March 8 she had a severe pain in the throat and arms which lasted five or six hours. She remained in bed for ten days after the attack. For two months previous to her admission to the hospital the patient had attacks of palpitation of the heart, associated with a feeling of flatulence and with an aching feeling in the arms. During the five weeks previous to admission the attacks of cardiac palpitation became more frequent, occurring about four

times a week. They seemed to be precipitated by "eating when tired," and reclining after meals lessened the attacks. A severe attack of palpitation caused her to enter the hospital.

On examination the patient appeared very healthy. She was not in distress and was very well nourished. There was slight cyanosis of the lips, mucous membranes and nail beds, and she was slightly dyspneic. The heart was beating regularly at a rate of 74. The apex-beat was not seen or felt. The outline of cardiac dulness extended 4 cm. to the right and 11.5 cm. to the left of the midsternal line. The heart sounds were faint and no murmurs were heard. The systolic blood-pressure was 130 mm. Hg and the diastolic pressure was 90 mm. Hg. The fluoroscopic examination revealed "a somewhat enlarged heart." The abdomen was somewhat distended. There was a slight anemia. The urine showed a very slight trace of albumin and many hyalin and a few granular casts. No other findings of importance were noted. The Wassermann reaction was negative.

On the morning after admission the patient had an attack of palpitation similar to her previous ones. It began and ceased suddenly, lasting about half an hour. The heart-rate was 180 per minute. During the patient's stay in the hospital the pulse was often noted as irregular and electrocardiograms showed that the arrhythmia was caused by interpolated premature ectopic beats of ventricular origin. The regular Q. R. S. groups were narrow. An attack of palpitation was brought on by exercise. Electrocardiograms showed ventricular paroxysmal tachycardia.

She left the hospital on November 27, 1915, feeling much improved, and was able to take care of her husband through an attack of pneumonia during the winter without discomfort. During the spring, about six months after leaving the hospital, she fell dead, apparently without any premonitory symptoms.

Case IV.—Hospital No. 8330: A laborer, aged forty-nine years, was admitted to the hospital April 25 from the out-patient department for tachycardia and pain in the chest. He gave a history of syphilitic infection at the age of seventeen. He had used alcohol moderately and had had several attacks of acute rheumatic fever. He also gave a history of one previous attack of palpitation of the heart. He said that six days previous to admission he was taken ill suddenly with a sharp pain in the chest on reclining, which was followed by a thumping of the heart and a choking sensation. He vomited and was unable to sleep. His heart became quiet in two days, but on attempting to walk to his place of work the cardiac symptoms returned and persisted until and after his admission to the hospital, three days later.

On admission he presented an anxious expression, with slight cyanosis of the lips, ears and nail beds. His face was of ashy hue. There was slight

engorgement of the veins of the neck and moderate dyspnea, with Cheyne-Stokes breathing. Moist rales were heard over the bases of both lungs posteriorly.

Over the heart in the region of the apex and in the epigastrium a fluttering or tremulous movement was seen. The cardiac dulness extended 4.5 cm. to the right and 12 cm. to the left of the midsternal line. Both heart sounds were distinct at the base and embryocardiac in character. The heart-rate was 230 to 240 per minute. Only one heart sound could be heard at the apex. The heart-rate could not be altered by pressure over either vagus nerve or by ocular pressure. The systolic blood-pressure was 80 mm. Hg. The diastolic pressure 68 mm. Hg. The abdomen was distended and rigid. The liver extended 7 cm. below the costal margin, felt smooth and was very tender. The pupils reacted sluggishly to light. The knee-jerks and Achilles tendon reflexes were exaggerated, equally so on the two sides. A "seven-foot" *x*-ray plate showed what was interpreted as an extreme degree of aortitis. The Wassermann reaction of the blood was negative while the spinal fluid gave a moderately strong positive reaction.

Electrocardiograms taken soon after admission revealed ventricular paroxysmal tachycardia. The tachycardia ceased two days after his admission to the hospital, but recurred and continued with a brief intermission for seven days, having been apparently continuous for five days. At the time of cessation of the tachycardia the heart-beat was irregular for a short period, but when electrocardiograms were obtained the heart was beating regularly at a rate of 82 per minute. There was no delay in $A-V$ conduction, while the T wave was inverted in all leads.

With normal rhythm diastolic and systolic murmurs arising at the aortic orifice were heard and a thrill could be felt over the second right interspace. The patient was found to have a right-sided hydrothorax, which was drained. He remained in the hospital for one month and antisyphilitic treatment with salvarsan and mercury was instituted and has been continued. The patient can now carry on light work and has had no return of tachycardia.

During his stay in the hospital numerous electrocardiograms were obtained and changes in the T wave were observed. All leads showed an inverted T wave for the first five days after the cessation of tachycardia. Then the T wave of the third lead had become upright. On the following day the T wave of the second lead became flat instead of inverted. Twenty days later the T wave of the first lead was flat while that of the other leads were upright. No digitalis was administered. Records made at intervals since the patient's discharge from the hospital shows normal electrocardiograms with upright T waves in all leads. This change in the T wave resembles certain findings of Smith after coronary ligation and also those

observed by Herrick in a case of coronary thrombosis which he reported. These changes may be taken as a probable indication of myocardial disturbance, possibly secondary to an interference with the coronary circulation.

Discussion. The four cases which have been described present sufficient evidence in our opinion to warrant in each instance the diagnosis of paroxysmal tachycardia of ventricular origin. They were all observed during periods when the heart-rate was from 170 to 228 per minute. These rapid rates occurred in paroxysms, and periods of relatively slow cardiac rate were observed in each instance. The transitions between the very rapid and relatively slow rate were as far as observed always sudden.

That the tachycardia was caused in each case by a very rapid succession of impulses arising in one of the ventricles was determined by electrocardiograms obtained during the paroxysms and during the periods of relatively slow rate. The ventricular complexes in all records during paroxysms are strikingly abnormal, and differ markedly from those obtained between attacks. None of the records taken during relatively slow rate show ventricular complexes which are characteristic of disturbances in the main branches of the intraventricular conducting system. The ventricular complexes of the tachycardia records from all cases resemble those which are obtained when impulses arise in the ventricles, either by single spontaneous ectopic impulse formation or by direct electrical stimulation of the exposed ventricles in animals. In the last case the complexes resemble those produced by ventricular contractions arising from stimulation of the right ventricle, while the curves from the other three cases suggest that the ectopic impulses originated in the left ventricle.

In two of the cases, the second and fourth, definite evidence of auricular contractions occurring at a slower rate than that of the ventricles is seen in the electrocardiograms, waves denoting auricular contractions being present. In the other two cases evidence of auricular activity during the tachycardia is somewhat uncertain.

The electrocardiograms taken between the paroxysms of tachycardia show definite abnormalities in all cases. In the first and second cases the ventricular complexes are unusually small and

deformed. They resemble the complexes seen in the case of coronary thrombosis reported by Herrick and those from another case of coronary thrombosis, confirmed at autopsy, from which we obtained electrocardiograms. The T wave is inverted in all leads in Cases III and IV, in the first lead in Case I, and in the third lead in Case II; the Q-R-S group of waves is not unduly prolonged in any of the cases. The curves from all these cases present evidence of myocardial damage, either from the form and size of the ventricular complexes (Cases I and II) or from the inversion of the T wave in all leads (Cases III and IV).

The relation of coronary occlusion to ventricular paroxysmal tachycardia is a point of special interest in regard to the cases that have been reported and to the phenomena generally. As has been pointed out, this relationship has been established for animals under experimental conditions. In our first case, where a thrombosis of the left descending coronary was demonstrated at autopsy, the tachycardia was apparently the result of changes brought about by occlusion of the coronary artery.

In the second case the patient's history is very suggestive of coronary occlusion, especially the sudden onset of the illness with severe pain in the region of the heart radiating down the left arm. This primary attack and several that followed it were typical of angina pectoris, so often associated with coronary artery disease. There was no definite evidence of syphilis, but chronic nephritis, arteriosclerosis and hypertension existed.

The third case is perhaps the one in which there is the least evidence of a lesion in the coronary arteries. The history of this patient, which is given in some detail, is suggestive of relatively mild attacks of angina pectoris. The fact that she never became pregnant during her long married life suggests that she may have had syphilis. The most significant fact, however, is her sudden death, which apparently occurred without premonition. Such an occurance is certainly suggestive of sudden heart failure, especially of ventricular fibrillation, which in turn points toward a lesion of the coronary arteries.

In the fourth case a definite history of syphilis with an extensive lesion of the aortic orifice is very suggestive of a lesion involving

the coronary vessels, especially at their origin. Our first case is, we believe, the first instance in the literature where direct evidence of the association of ventricular paroxysmal tachycardia with coronary occlusion has been obtained, although in two other cases which have been studied by others lesions of the coronary arteries may have been causative factors. We have recently observed two cases which showed occlusion of the coronaries at autopsy, neither of which had tachycardia of high grade.

Conclusion. Four cases of paroxysmal tachycardia of ventricular origin are described. The diagnosis of this condition depends on the interpretation of electrocardiograms, and certain features necessary for this diagnosis are discussed.

The relation between this condition and occlusion of the coronary vessels has been proved in animals. This relationship, although not constant, exists in some of the cases of ventricular paroxysmal tachycardia in man. This relationship is definite in the first case here reported, which was studied at autopsy, and is probably present in all of our cases.

The prognosis of paroxysmal tachycardia of ventricular origin is more unfavorable than that of auricular origin, and the differentiation of the two types is of practical importance.

We wish to thank Dr. M. T. Burrows for the pathological study of our first case.

Electrocardiograms and photographs will be published in *Heart*.

RETROGRADE STRETCHING IN THE TREATMENT OF IMPERMEABLE CARDIOSPASM

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A FEW years ago I described 2 cases[1 2] of impermeable cardiospasm successfully treated by retrograde stretching by means of the pyloric dilator. Inasmuch as these cases are not very common and present rather considerable difficulty in their treatment I thought it of interest to report a few cases and discuss their management.

As regards the term "impermeable cardiospasm," it signifies, as is well known, failure of food to enter the stomach in the normal way, absence of organic stricture, and impossibility of reaching the stomach by the usual gastric tube or a bougie.

Experience teaches that two groups of impermeable cardiospasm may be discerned:

1. The bougie nearing the cardia engages in the sacculated wall of the esophagus, and here meets with a slight resistance. If one tries to push the bougie farther in, one has the sensation as if one pushed the thin elastic wall further down. This may be done gently without much force, when one distinctly feels the esophageal wall being pushed down and coming up again following the olive end of the bougie.

2. The bougie strikes the cardia but fails to enter it. Here again two varieties are encountered: (*a*) The bougie meets with a distinct resistance and cannot be pushed any further (spasm and fixation of cardia; (*b*) the bougie meets with a resistance at the cardia, failing to pass it; it can, however, be pushed further down for two or three inches, moving the closed cardia for that distance into the stomach, without entering the lumen (movable cardia).

An illustration of group 1 is given by the following case which I observed very recently:

Case I.—November, 1919. B. R. P., aged forty years, had grippe about ten months ago. Thereupon the patient began to suffer from distress in his epigastrium pretty soon after eating. Patient noticed difficulty in swallowing liquid and solid foods. He felt as if the food collected at the pit of the stomach; and he was unable to force it down

Fig. 1.—Roentgenogram of the esophagus of B. R. P. after the injection of bismuth; the esophagus shows diffuse dilatation and the cardiac opening lies away from the center.

without water and without much straining at that. Then after such effort, he would feel the food suddenly drop down into the stomach.

For the last four months vomiting occurred almost every day, large quantities being brought up at once without much effort. Occasionally the patient wakes up at night with constriction in the chest and vomiting. For the last three months he has noticed that he could not partake of ordinary food without the help of water. He experiences difficulty in eating and pains in the scrobiculus. For the last six weeks no food whatever has agreed with the patient, almost everything being vomited

during the day or night. He has lost 20 pounds during his sickness, especially during the last four months. He feels extremely feeble and can hardly walk. Examination of the patient fasting—showed that the esophagus contained 300 to 400 c.c. of undigested food, which appeared through vomiting. A bougie (No. 43) entered 17 or 18 inches and struck the esophageal wall, as evidenced by a feeling of elasticity of the wall upon pushing the bougie gently further in, but did not pass the cardia. Swallowing sound was absent.

FIG. 2.—Roentgenogram of B. R. P. with the duodenal tube in place. There is some barium in the stomach; the tube end lies in the beginning of the small intestine.

Based upon these findings the diagnosis of a dilated esophagus and impermeable cardiospasm was made and patient was referred for further observation to the Lenox Hill Hospital. The duodenal bucket passed the cardia and entered the duodenum in twenty-four hours. The string showed bile below 24 inches and a blood stain at 17 inches. The test apparently showed the presence of an ulcer of the stomach near the cardia, which was probably the cause of the cardiospasm.

An *x*-ray picture of the esophagus taken by Dr. Thomas Scholz corroborated the diagnosis of dilatation of the esophagus, due to cardiospasm.

FIG. 3.—Roentgenogram of B. R. P., showing the pyloric dilator; the inflated balloon is just in front of the cardia in the stomach.

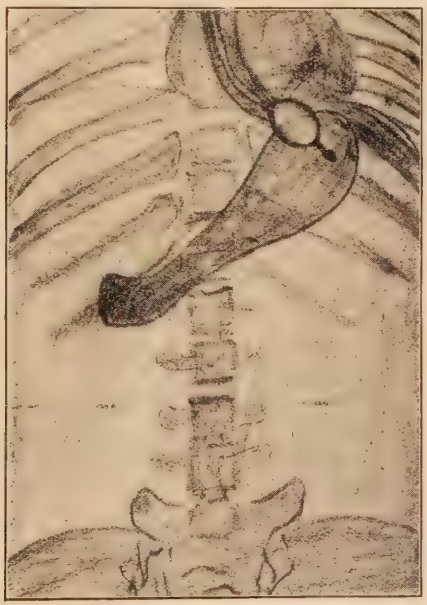

FIG. 4.—The same as Fig. 3; the dilator has been pulled up about 2 inches or more without passing through the cardia, the latter being simply lifted and invaginated into the esophagus.

In order to cure the ulcer and to afford relief to the dilated esophagus it appeared best to keep the patient on duodenal alimentation. The tube was introduced in the afternoon of October 20, 1919, and the following day feeding by the tube through the duodenum was commenced. The patient felt much relieved and strengthened within a few days. There was no vomiting and he slept well. After eight days of duodenal feeding the tube was removed. October 28, 1919, the pyloric dilator was introduced. On the following morning the balloon of the instrument was found

Fig. 5.—The same case as shown in Fig. 4; the balloon of the dilator has passed the cardia and is within the esophagus.

to be in the duodenum. Stretching of the pylorus and then of the cardia (up to 60 F.) was then easily performed.

During the month of November, 1919, stretching of the cardia was undertaken every other day, a balloon of 70 F. passing through without much difficulty. Patient could eat quite well and did not vomit. He gained considerably in weight.

Figs. 1 to 5 show the dilated esophagus of the patient P., with the cardiac opening lying to the side, away from the center, and the different steps of the method of retrograde stretching by the pyloric dilator.

It was soon discovered that after a few stretchings with the pyloric dilator, bougies could now be introduced and reach and pass the cardia.

The usual metal cardiodilator was then introduced for further treatment, and the cardia was stretched twice up to 80 Fr. and ultimately to 110 Fr. The patient could now eat like any ordinary individual without experiencing the slightest inconvenience.

Fig. 6.—The inflatable dilating bougie.

Group II, subdivision *a*, may be represented by the following case:

Case II.—March 17, 1919. Mrs. A. R., about forty years of age, has suffered from difficulty in eating, choking and vomiting for the last twelve years. Frequently she would have to leave the table in the middle of a meal in order to eject the food, on account of a feeling of suffocation she experienced. She never could eat with ease like other people. She was forced to gulp down a quantity of water, in order to make the food go down. I saw the patient first during the spring of 1917.

The findings were as follows: Swallowing sound absent; bougie with olive No. 43 meets resistance, which is impassable, at 16 inches from the lips. This spot of resistance is stationary and cannot be pushed down, or made to move even a little bit. Olive No. 48 shows exactly the same condition.

During March, 1919, a chance for the reëxamination of patient presented itself. Again the findings were exactly the same: Swallowing sound absent; bougies with olives Nos. 38, 43 and 54 meet with an absolutely impassable resistance at 16 inches distance from the lips. The stomach tube introduced 16 inches into the esophagus in the fasting condition of the patient brings up 150 c.c. of food from the day before with the following characteristics: Reaction acid; No HCl present; rennet absent; lactic acid present.

The patient then entered the Lenox Hill Hospital for observation and treatment. The duodenal bucket entered the duodenum and showed on

the string a blood stain from 22½ to 23 inches from the lips; from 24 to the end it was stained a golden yellow.

A diagnosis of severe impermeable cardiospasm complicated by duodenal ulcer was made. The patient was kept on duodenal alimentation for two weeks. This afforded perfect rest to the dilated esophagus, stomach and the upper part of the duodenum.

After removal of the tube, the pyloric dilator was introduced, and after a night's sojourn, it entered the duodenum. The pylorus, and then the cardia were stretched retrogradely. This procedure was kept up for two weeks, both pylorus and cardia being stretched about twice a week. Thereafter stretching of the cardia alone was employed, first twice weekly, and later once a week. The patient made a rapid recovery, gaining in weight steadily and being able to eat almost all kinds of food like ordinary people.

Group II, subdivision *b*, is well represented by the following case:

CASE III.—December 10, 1919. Mrs. F. F., aged twenty-five years, married, no children, menses normal. She had scarlet fever as a child—good recovery; operated upon for goiter at the age of nine.

The present history dates back to four years ago, when the patient was suddenly frightened and fainted. After this for about some time she had a fear of people. This lasted about one year and cleared up. This was followed by pain in left iliac fossa, at first, and then by pains all over the body. The patient was unable to eat, and had great difficulty in swallowing. She had a choking sensation in her throat continuously—whether she ate or not. Two years ago vomiting began. The patient would vomit during meals and between meals. The vomitus at times contained undigested food and at other times consisted only of mucus—never any blood.

When the patient would eat, she would feel as though the food was going to choke her. At times the food would go into the stomach and again it would not go beyond the mouth. But the patient would vomit even though no food entered the stomach. The bowels were constipated.

For the past four months two to three days would elapse during which the patient could not eat; even water was swallowed with difficulty. The bowels were constipated during the past three or four months for a week at a time, unless she took an enema. The pain was very severe in the epigastrium for the past few months. The patient slept well during the entire period of her illness. She lost 36 pounds in the past four years, most of which was lost in the past six months, though just how much the patient does not know.

The physical findings were as follows: Swallowing sound absent. Bougies 38 and 43 meet with a resistance at 16½ inches from the teeth.

Upon pushing the bougie further down, the resistance (cardia) can be moved for fully 2½ to 3 inches downward, the bougie failing to pass through the cardia. A stomach tube, introduced 15 inches from the teeth, into the esophagus of the fasting patient brings forth about 120 c.c. of food residue, showing the following: HCl absent, lactic acid present, rennet absent.

The diagnosis of movable cardia and impermeable cardiospasm was made, and the patient was referred to the Lenox Hill Hospital for further examination and treatment.

The duodenal bucket was introduced, atropin being given, and entered the duodenum over night. The string showed bile beyond 24 inches and a blood stain at about 18 inches. The patient was then given the duodenal tube with atropin medication. The next day the tube entered the duodenum. She was then treated by duodenal alimentation for two weeks. She felt well, vomited very little during the entire period of treatment and picked up in strength.

After the withdrawal of the tube, the pyloric dilator was introduced and with it liquid food by the mouth and atropin were given. The next day the pyloric dilator was found to be still in the esophagus above the cardia. It was left in the digestive tract for another period of twenty-four hours. When examined forty-eight hours after its introduction the dilator was found to be in the duodenum. Stretching first of the pylorus and then of the cardia was now easily accomplished. While, however, we could pull through the pylorus a balloon corresponding to No. 65 Fr., the cardia did not at first permit a larger balloon than No. 50 Fr. A few days later, however, we succeeded in pulling through a No. 60 Fr.

After these retrograde stretchings the patient could eat with gre ter ease and vomited but seldom. Her esophagus was washed out every other night. At first 100 c.c. of food residue would be found; later on the amount was 50, and ultimately 40 c.c.

A new attempt was then made to pass a bougie through the cardia, for it was believed that the spasm was much diminished. This proved correct. At first we succeeded in passing bougie No. 48 through cardia after pushing it down 18½ inches. A few days later bougie No. 54 passed the cardia in the same manner as No. 48 and entered the stomach.

Later on, for the retrograde stretching in this particular case, we made use of a new instrument which resembles the aspirating bougie, namely, the "inflatable dilating bougie."

The patient has gained 12 pounds in weight since we succeeded in stretching her cardia and eats fairly well.

I herewith give a drawing of this cardiodilator, the construction of which is apparent and needs no description. The advantage of the inflatable dilating bougie is that it can be introduced at

once into the stomach, without a period of waiting which is necessary with the pyloric dilator, and the stretching performed immediately after inflating the balloon. (See Fig. 6.)

I have observed a few more cases belonging to the two groups just described. I shall refrain, however, from recording them as they would be almost a repetition of the cases above detailed.

Altogether I have had 10 benign cases of impermeable cardiospasm. Two (about eight or ten years ago) had been operated upon by Dr. Willy Meyer; in 1, Mrs. P., an esophagoplication was made with great benefit to the patient for about six months, when later she succumbed to an empyema. The second patient, a Mr. D., was in such extremis when first seen by me, that a gastric fistula was the only feasible procedure to begin with. He died as a result of perforation of the esophagus occurring a few days after the establishment of the fistula.

The other eight had all been treated by retrograde stretching of the cardia, some after a previous course of duodenal alimentation. All of these patients benefited greatly by retrograde stretching. They could eat with greater ease and did not vomit as much. In some of them after a few stretchings the cardia became accessible to direct treatment (*i. e.*, the impermeable cardiospasm was converted into a simple permeable cardiospasm).

There are a few points concerning impermeable cardiospasm I would like to broach.

1. As regards the etiology of impermeable cardiospasm, as well as of plain permeable cardiospasm, gastric ulcer, especially if situated near the cardia, seems to play a dominant part. In the new cases here described as well as in a great number of others, observed in my practice, I have found the association of the two conditions present. What is more natural than to assume that the ulcer is the original cause of the persistent spasm? In this connection I would like to mention another point which relates to the connection of peptic ulcer and cardiospasm.

In cardiospasm the swallowing sound at the cardia is always absent. In a number of patients with ulcers near or within the cardia I have found the swallowing sound absent, and this even in cases in which there was apparently no delay in the entrance of food from the esophagus into the stomach. Moreover, I know

of two patients who had cardiac ulcers years ago, which have healed perfectly, who have ever since shown an absence of the cardiac swallowing sounds. It seems as if the ulcer near the cardia by its presence, and later by its healing, interfered with the normal function of the cardia. While the food may pass through this opening in due time, still the normally heard sounds are no longer present, probably because of some alteration in the structure of the cardia.

The absence of the swallowing sounds in some cases of ulcer near the cardia again show the intimate connection between gastric ulcer and interference with the normal work of the cardia.

2. The diagnosis of benign impermeable cardiospasm is usually quite easy to establish. In group 1, that of sacculation of the esophagus with the opening lying somewhat away from the center, the bougie strikes the esophageal wall at the bottom. This can be pushed down a little, giving the sensation of a thin elastic pliable membrane. Extreme caution is required in the performance of this test, as forcible pushing of the bougie might penetrate or injure the esophageal wall.

In group 2, subdivision *a*, there is often the thought of a neoplasm presenting itself. For the bougie meets with an impassable resistance at about 16 inches which at first sight simulates a growth. There are, however, the following features which will help to establish the diagnosis: In benign cardiospasm there is usually a long history of trouble, two to ten years or more. There are besides frequent intermissions during which patient partakes of food pretty easily. In a real neoplasm there is a comparatively short history of a steadily progressing trouble, without any periods of freedom. The duodenal bucket and frequently the pyloric dilator enter the stomach after a night's sojourn in the digestive tract. Usually it is possible to pull from the stomach through the cardia a balloon measuring in size 55 to 60 mm. in circumference, if not more. In cancer, these attempts will remain unsuccessful. The *x*-rays will frequently likewise help to establish a correct diagnosis, with some exceptions.

3. As regards treatment retrograde stretching with the pyloric dilator appears to be preferable to passing bougies over a previously swallowed string. It sometimes happens that even a

flexible instrument cannot follow the string, if there is present too great a bend in the sacculation or an unyielding spasm at the cardia.

In cases in which an ulcer in the stomach is suspected or really discovered, it is advisable first to accord the esophagus and stomach a period of rest (by duodenal alimentation) before instituting the stretching treatment. The latter is best done first by the pyloric dilator, every other day or twice a week, the dilator being introduced before retiring supplemented by a dose of atropin, and the stretching done the following morning. After a few stretchings the dilator enters the stomach in a much shorter time. It can then be passed early in the morning, with atropin, and stretching performed one or two hours later, as soon as the balloon has reached the stomach. This can be easily ascertained either by the *x*-rays or by inflating the balloon, and then pulling it upward. In case the balloon is in the stomach a resistance is felt as soon as the instrument reaches the cardia. If no resistance is encountered, the balloon is deflated the patient given some water or tea to drink, and after waiting one-half hour or so, the experiment is repeated. The entrance of the balloon into the stomach must be patiently watched and tested, and when found in the latter retrograde stretching can be undertaken.

Stretching *in situ* can also be done by the double balloon pyloric dilator. This is more effective but the instrument is somewhat coarse and harder for the patient to manage.

In some of the cases treated after a few retrograde stretchings the cardia becomes accessible to direct instrumentation. In these instances the usual method of stretching can be carried out by the common instruments in use for the dilatation of the cardia.

In some cases of marked cardiospasm with considerable dilatation of the esophagus, besides the stretching, the esophagus was washed out every night or every other night. This gives much relief to the patient and is also of value with regard to gauging the improvement. As soon as there is a real change for the better, the amount of residue in the esophagus becomes less and ultimately disappears.

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INVOLVEMENT OF THE AURICLE AND CONDUCTION PATHWAYS OF THE HEART FOLLOWING INFLUENZA

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During the past year a number of interesting postinfluenzal cardiac conditions, late results of the 1918 influenza epidemic and more recent complications of the epidemic of 1920 have been observed and studied in the electrocardiographic laboratory of the Michael Reese Hospital. Certain of these cases throw light on the mode and site of action of the influenza poison on the cardiac mechanism, particularly on the auricle and conduction system, and clarify, to some extent, the more general statements of observers in the earlier epidemics. It is for this reason that the following cases are reported.

A number of suggestive studies have already appeared, Lucke, Wight and Kime[1] from a detailed study of necropsies from 126 definitely proved fatal cases of influenza, concluded that in the majority of instances acute parenchymatous changes of the myocardium, similar to the changes of other acute infectious diseases, occurred. In over 90 per cent. of these cases more or less relaxation of the right heart was present; in over 88 per cent. an associated cloudy swelling occurred. Microscopically they found acute parenchymatous degeneration and vacuolization. While these cases represented the fatal ones it may be inferred that in the less seriously ill patients the heart is similarly affected, though to a less degree.

[1] Pathologic Anatomy and Bacteriology of Influenza, Arch. Int. Med., 1919, xxiv, 154.

Other reports, although not as conclusive as the above, admit some degree of myocardial involvement. For example, Hart,[1] although believing that the cyanosis and death in influenzal bronchopneumonia is not primarily cardiac in origin, admits that in the few uncomplicated cases in which the heart was carefully studied a moderate degree of myocardial degeneration was found. Smith,[2] in a study of postinfluenzal tachycardias at Camp Travis, concluded that organic heart disease was not the basis of the tachycardia and quotes various autopsy reports from army camps as to the infrequence of myocardial involvement, judged largely from gross appearances. Later, however, he states, "It is possibly true that pathologic changes, sufficient to cause serious disturbances in later life, could have easily been overlooked with the naked eye."

A somewhat similar conflict between clinical and necropsy findings may be found in Sir James Mackenzie's discussion of "Cardiac Complications of Influenza,"[3] wherein he states that "if one looks at the heart postmortem in these fatal cases one sees the extensive damage done to the myocardium," and continues, "It is possible that influenza may lay the beginnings of a myocarditis which ultimately leads to heart failure, but I have not seen this occur in the many cases I have met in general practice." He concludes, in reference to the late effects: "The weakness after influenza is not, properly speaking, cardiac in origin, but is the outcome of an injury to other systems as well as the heart, such as the central nervous system. Even when we find such marked abnormalities as increased rate, systolic murmur, increase of size of heart and extrasystoles the cause of these signs ought not to be looked upon as heart disease, but merely as manifestations of general illness." In reference to the effect of influenza on patients with chronic heart disease, Mackenzie states, "I never found that influenza injured them in any way. Everyone, even those with advanced heart failure, passed through the attack scathless."

[1] The Heart in Bronchopneumonia: Observations on the Activity of the Heart and its Response to Digitalis Made during the Recent Epidemic, Am. Jour. Med. Sc., 1919, clviii, 649.

[2] Tachycardia Following Influenzal Pneumonia, Jour. Am. Med. Assn., 1919, lxxiii, 1685.

[3] Cardiac Complications of Influenza, Practitioner, 1919, cii, 19.

Thomas Lewis,[1] however, takes issue with Mackenzie in the following words: "The relation of infection to the cases of real heart disease must also be emphasized. It is of first importance. Nothing jeopardizes the condition of a heart patient more than infection, be the infection rheumatic fever or infection expressed as tonsillitis, influenza, bronchitis, etc. During the recent influenza epidemic the infection spread to a ward reserved for cases of serious heart disease. We lost two patients, and the lives of several others were seriously jeopardized."

These several studies are sufficient to emphasize the diversity of opinion regarding the effects of influenza on the heart, notwithstanding which some degree of uniformity of opinion is beginning to crystallize and may be expressed as follows:

1. Necropsies of fatal cases of influenza, in spite of slight gross pathologic changes in the heart, show rather universally acute parenchymatous degeneration and vacuolization, and, at times, extensive myocardial damage. Group I.

2. Clinical studies during the acute stage of illness, and in convalescence, indicate a rather remarkable recoverability of complete cardiac function. The postinfluenzal flabby heart muscle gradually disappears under graduated and properly directed exercise. Several of our cases are of this type. Group II.

3. Certain of these acute myocardial processes, however, do not clear up, at any rate for a very long time, and become cases of true postinfluenzal myocardial insufficiency. The present cases for the most part fall into this last group. Group III.

A very few electrocardiographic studies in influenza have appeared. Cockaynes'[2] description of heart-block and bradycardia is of special interest in this connection. He found that simple bradycardias were caused by a poisoning of the myocardium, especially the sino-auricular node; the cases of heart-block result from the poisoning of the muscle of the auriculoventricular bundle; while two cases of marked bradycardia with prolonged A–V interval were due to the

[1] The Soldier's Heart and the Effort Syndrome, New York, 1919.

[2] Heart-block and Bradycardias Following Influenza, Quarterly Jour. Med., 1919, ixi, 409.

involvement of both sino-auricular and auriculoventricular areas. He reports one boy, aged sixteen years, with sinus block, who had a mild right-sided postinfluenzal pneumonia that cleared up entirely in twenty-eight days. The prolonged *A–V* ("P–R") cases appeared in mild pneumonias and lasted from nine to twenty-three days.

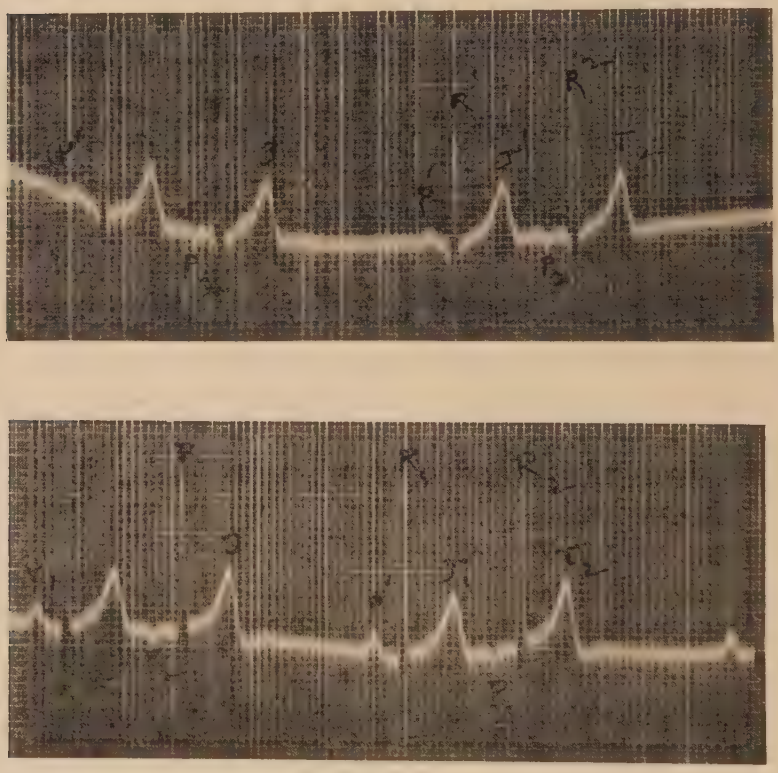


FIG. 1.—Case I. S. R. Postinfluenzal myocarditis. Pulsus bigeminus caused by regularly recurring auricular extrasystoles—ectopic—(inverted) auricular contractions (P_2) following normal contraction of the auricle (P_1).

Nine cases of two to one heart-block were observed, lasting from one to thirty-three days. Six cases of three to one heart-block averaged fourteen days. The onset of the bradycardia usually occurred after the temperature had become normal. Most of the patients were young men suffering from mild influenzal pneumonia. After six

weeks only one complained of cardiac symptoms. None showed any undue irritability of the heart.

Case I.—S. R., teamster, aged twenty-five years, married, entered the hospital August 20, 1919, complaining of moderate shortness of breath and precordial discomfort varying in intensity, necessitating, at times, rest in a recumbent posture. He was in robust health up to April, 1919, at which time he had a moderately severe attack of influenza, with temperature 101° to 102°. Against

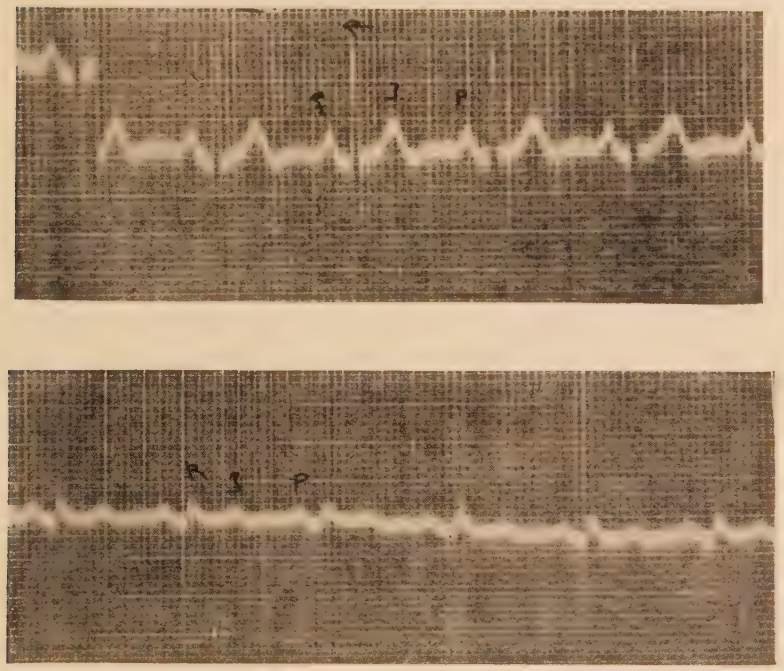


Fig. 2

the advice of his attending physician he remained home only three days, returning to his work as a teamster while not entirely free from fever. Two weeks later the above complaints occurred. He is a moderate smoker. Examination of his heart shows the apex in the fifth interspace, the left border 10 cm. the right 4 cm. from the mid-sternal line. Heart tones irregular, occurring in groups of two, pulsus bigeminus, no murmurs. His systolic blood-pressure was

115 mm. Hg, diastolic 55 mm. Hg. The urine was negative, blood negative and blood-Wassermann negative. Electrocardiographic examination showed a pulsus bigeminus due to regularly recurring auricular extrasystoles, "P" being inverted, "ectopic," every second auricular beat (Fig. 1). At the present (April, 1920), one year after his influenza infection, patient is able to take care of a small newsstand, to which occupation he was advised to change because of inability to work as a teamster. Recent examination at the dispensary showed a perfectly normal pulse when at rest, which, however, promptly changed to bigeminus following slight exertion, sitting up and lying down, on the examining table. Summary: Postinfluenzal auricular myocarditis, pulsus bigeminus, auricular extrasystoles. Group III. Duration twelve months.

Case II.—Dr. S., Mobile, Alabama, aged thirty-eight years, physician. He entered the Medical Reserve Corps of the army in June, 1918. In October he had a moderately severe attack of influenza, without pneumonia, but with complicating frontal sinusitis. Since the influenza he has noticed a slight dyspnea, particularly on playing golf. He believes his endurance low and notices that he tires easily. When previously he was able to work without fatigue from seven in the morning to twelve at night he now scarcely can get through his day from eight in the morning to three in the afternoon. He still complains of frontal headache. There is no precordial pain or edema of the ankles. His systolic blood-pressure is 150 mm. Hg, diastolic 90 mm. Hg. His right heart measures 3 cm., his left $11\frac{1}{2}$ cm. from the midsternal line. The pulse was 88, the heart tones regular and clear; there were no accentuations or murmurs. Immediately after exercise his pulse increased to 132, after two minutes to 128, after five minutes to 112 and after ten minutes to 100. His urine showed two plus albumin, microscopic negative; leukocytes 6800. The electrocardiographic examination showed "P" high in L. I, II. and "R" low and notched in L. III. (Fig. 2). Diagnosis: In view of the poor response to effort, marked fatigue, dyspnea, albuminuria and electrocardiographic findings a diagnosis of postinfluenzal myocardial insufficiency. Group III. Duration fourteen months.

Case III.—C. H. W., aged thirty years, merchant, had a mild attack of influenza in September, 1918, and a recurrence in November, 1918. In neither attack, although there was a rise of temperature, did he take to his bed. Following the last attack he noticed a marked loss of endurance and an irregularity of his pulse. Examination of his heart was entirely negative except for an occasional extrasystole before exercise at long intervals. Exercise tests

(hopping fifty times on one foot) showed a pulse of 93, systolic blood-pressure 122 mm. Hg, diastolic 75. Immediately after exercise

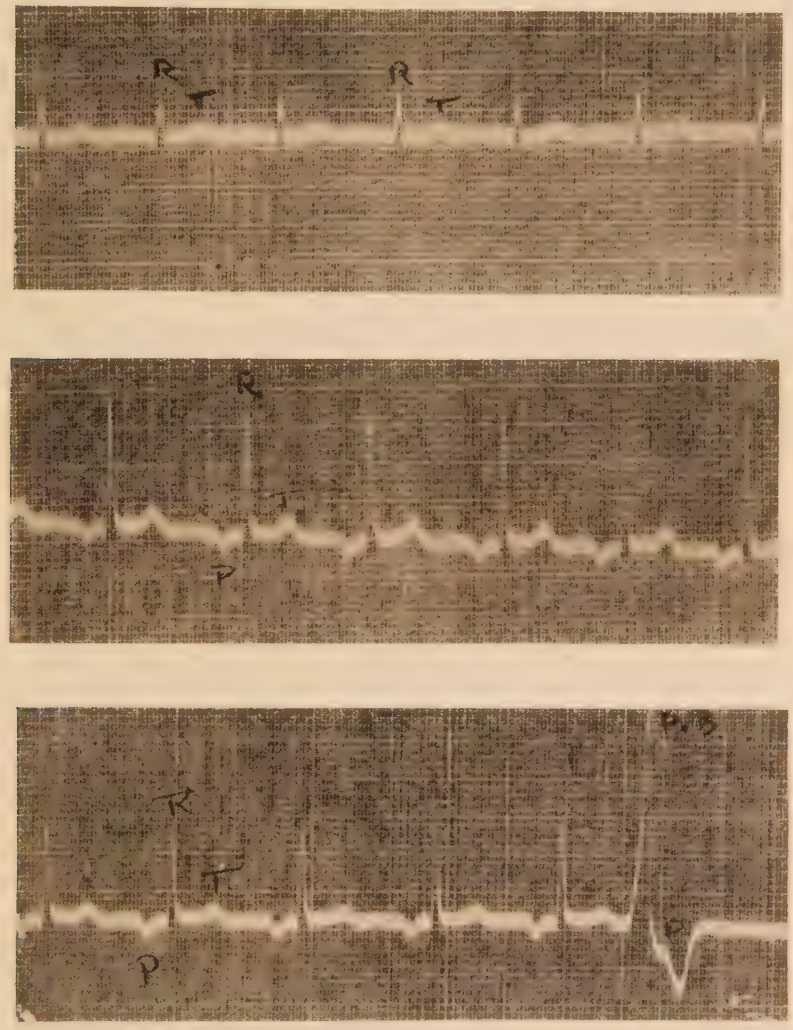


Fig. 3

the pulse was 126, systolic pressure 135, diastolic 65. Two minutes after exercise the pulse was 95, systolic pressure 118, diastolic 65. Electrocardiographic examination (Fig. 3) shows absence of "P"

in L. I. and inversion of "P" in leads 2 and 3, extrasystole of right ventricular origin in L. III. Diagnosis: In view of fatigue not felt before the attacks of influenza, extrasystoles and electrocardiographic findings a diagnosis of postinfluenzal auricular and ventricular involvement was made. Summary: Postinfluenzal, right ventricular extrasystoles and "ectopic" auricular contractions. Group III. Duration fifteen months.

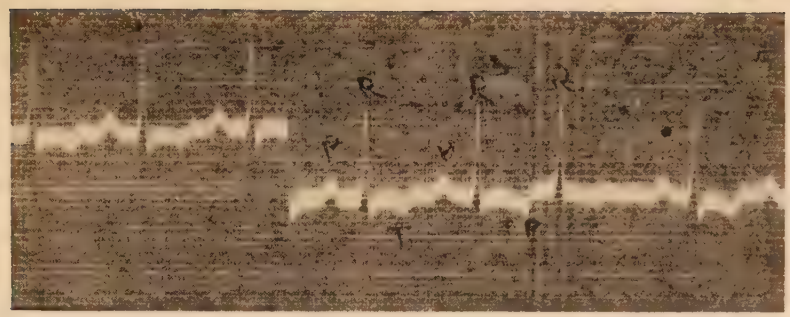
Case IV.—Dr. B., aged twenty-eight years, house physician, entered the hospital March 3, 1920, complaining of sore-throat, with a history of attendance on several nurses who had been on duty in the influenza wards and who had become ill, suffering with sore-throat, temperature and generalized pain. Dr. B. complained of pain in his knee-joints, palpitation, sensation of "heart stopping," moderate frontal headache and nasal discharge containing pure Streptococcus hemolyticus. The past history revealed the usual exanthemata of childhood and a moderately severe attack of rheumatism of three weeks' duration following sore-throat seventeen years ago. The mother died of a cardiac lesion at the age of thirty-three. The father had attacks of rheumatism. Examination showed a large, well-nourished, obese young man, lying quietly in bed without evidence of respiratory or cardiac embarrassment, with purulent nasal discharge. Examination of the heart showed no evidence of gross circulatory failure. The pulse-rate was seventy, with an intermittence about every thirty beats. The quality was soft and compressible, the apex fifth interspace, feeble, no thrill. The left border was inside the nipple line, the right border at the right sternal margin. The heart tones were soft and there was no murmur. There was no edema of ankles. March 4 the pulse was irregular and there was some swelling of the knee-joints and small joints of the feet. The electrocardiographic report (Fig. 4) showed moderate left preponderance, diphasic "P" in lead I, and auricular extrasystoles. P–R. .20, rate 109.

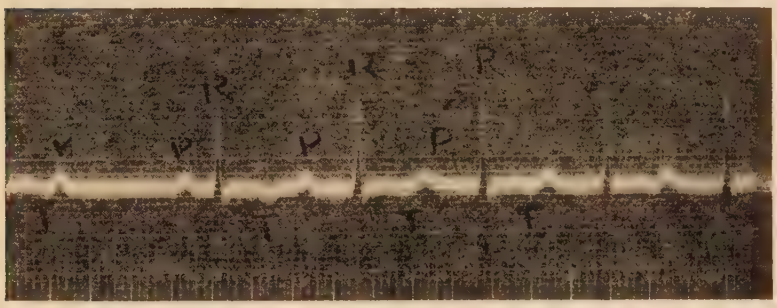
Electrocardiogram March 16 (Fig. 4) shows auricular extrasystoles, dropped beats, P–R .32 to .36. Rate 96. Progressive lengthening of P–R.

Electrocardiogram March 22 (Fig. 4) shows the blocking of an auricular extrasystole. P–R .24, rate 88.

Electrocardiogram March 26 (Fig. 4) shows P–R, averaging .24, pulse 90, auricular extrasystoles arising in the neighborhood of sino-auricle node. P. T. Superimposed. Electrocardiogram, April 20, shows normal cardiac mechanism.

Summary and Diagnosis: Acute streptococcus myocarditis involving particularly the auricle and conduction pathways produc-





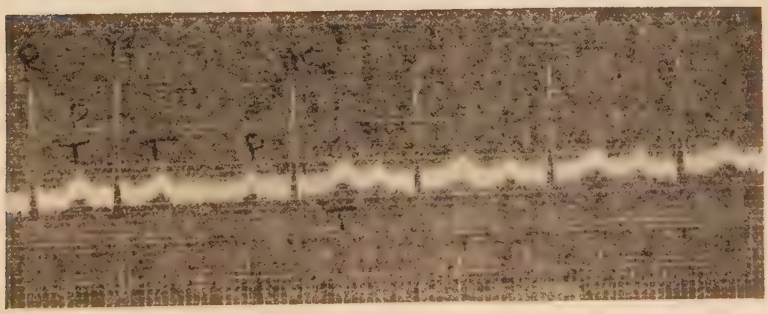


Fig. 4

ing chronologically, ectopic auricular extrasystoles; involvement of the auriculoventricular bundle with delay in the P–R interval and occasional dropped beats (early heart-block); blocking within the auricle of ectopic extrasystoles; auricular extrasystoles arising in the immediate neighborhood of the sinoauricular node. Group II. Duration six weeks.

Case V.—Miss E. S., pupil nurse, aged twenty-three years, entered the hospital March, 1920, complaining of sore-throat and loss of weight. Since a septic sore-throat December 19, 1919, containing hemolytic streptococcus, she had had more or less throat infection and felt weak on slight exertion and tired easily. Examination showed the hands and face to be very pale, anxious facies, apparently suffering, hands held over the heart, respirations shallow and superficial, pulse 114. She complained of gripping pain over the heart that made speech and breathing difficult. She said that she could feel her pulse become slow and irregular, after which attacks the pulse became more rapid. There was a marked tenderness in the fifth interspace. The apex lay within the nipple line in the third and fourth interspace. The heart tones were irregular. There were no murmurs. An electrocardiogram taken March 3 (Fig. 5) showed a three to two heart-block, rate 62 of the ventricle. An electrocardiogram taken the following day showed nodal rhythm, rate 89.5 (Fig. 5).[1] March 9 the heart seemed normal, there were no accentuations and the first sound was barely perceptible. The electrocardiographic examination showed P–R .25, rate 65.2. One week later examination showed normal cardiac mechanism. Summary and diagnosis: Acute streptococcus myocarditis involving primarily the bundle with three to two partial heart block, later nodal rhythm, with anginal attacks. Group II. Duration two weeks.

Case VI.—Miss H. N., stenographer, aged twenty-eight years, has had "heart trouble" since the "flu" in October, 1918. Remained in bed three weeks during attack; there were no lung complications, but some cardiac irregularity during acute illness. Remained home two months convalescing. In the spring of 1919 complained of same precordial uneasiness with slight pain, relieved partially by digitalis.

January, 1920, again complained of pain in heart region; no dyspnea or pain with effort; some palpitation. At times has some

[1] Dr. Robinson, who kindly looked over this curve, believes it more likely a markedly delayed *P–R* interval with *P* buried in the *T* complex.

throbbing sensation in left arm. Has lost six pounds past few weeks, tires easily, gets extremely fatigued.

Past Illnesses. Scarlet fever eight years ago. Inflammatory rheumatism at twelve years of age in knees and elbows; recurring tonsillitis; tonsillectomy five years ago.

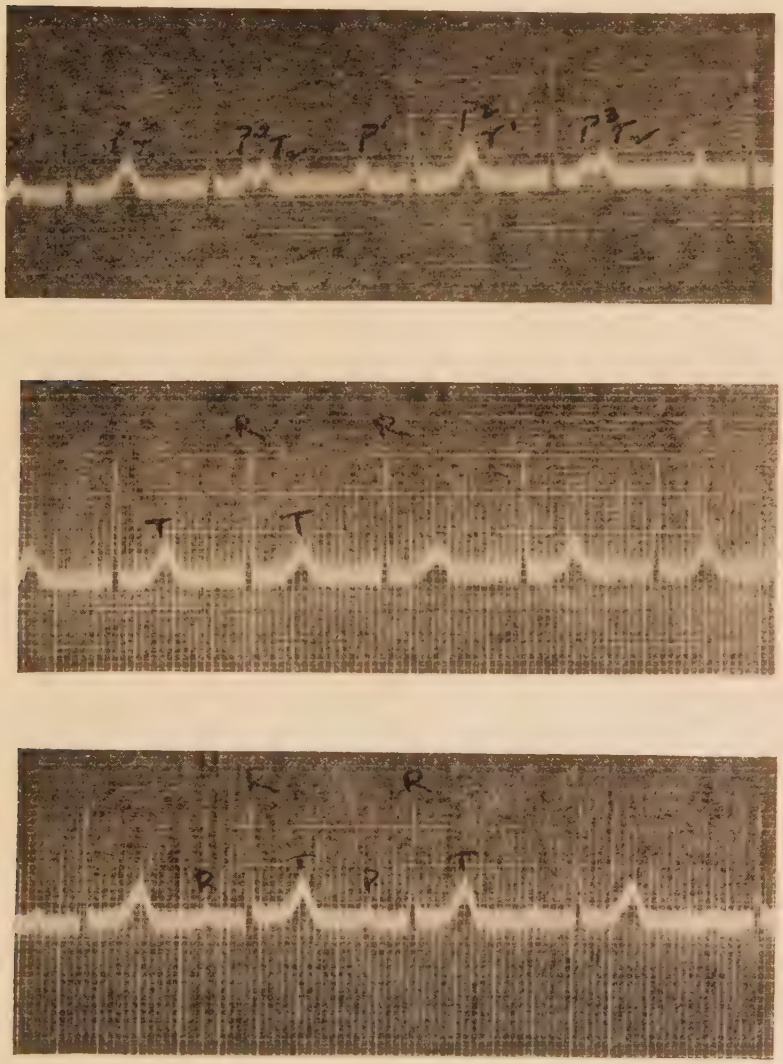


FIG. 5

Examination. Right heart 3½ cm. left 12 cm. midsternal line. Arrhythmia (extrasystoles) left border just outside nipple line.

Electrocardiograph. Auricular extrasystoles in all leads arising in neighborhood of pacemaker, number possibly increased after atropine.

Summary. Chronic postinfluenzal myocarditis, with localization in the auricle, resulting in auricular extrasystoles. Duration seventeen months. Group III.

Discussion. The above cases, cited as examples from a larger group, are offered as evidence that the acute epidemic respiratory infections known as influenza, cause damage to the cardiac mechanism, which may be demonstrated clinically and electrocardiographically. As observed by the latter method these infections affect, for the most part, the auricle and conduction pathways of the heart, although clinically it may be supposed that ventricular involvement also occurred. Unfortunately no gross or microscopic pathologic material was available for study. Cases IV and V, in which hemolytic streptococci seemed to be the predominant etiologic organisms, are strikingly similar to Cockayne's cases of influenzal poisoning of the sino-auricular node and auriculoventricular bundle, thereby substantiating the influenzal involvement of the auricle and the His bundle.

One feels justified in concluding that at least in a certain percentage of cases, acute influenza (streptococcus) picks out early and to a degree exclusively the auricle and conduction pathways. Barker's[1] recent interesting case of arrhythmia with auricular involvement following focal infection may still further broaden our views as to the general point of attack of infectious agents and poisons on the cardiac mechanism.

Conclusions. 1. Six cases of postinfluenzal myocardial involvement are reported, involving particularly the auricle and conduction pathways of the heart.

2. From a survey of the literature together with clinical and electrocardiographic studies, a grouping of postinfluenzal cardiac complications is offered as follows:

[1] Cardiac Arrhythmias, Arch. Int. Med., 1919, xxiii, 158.

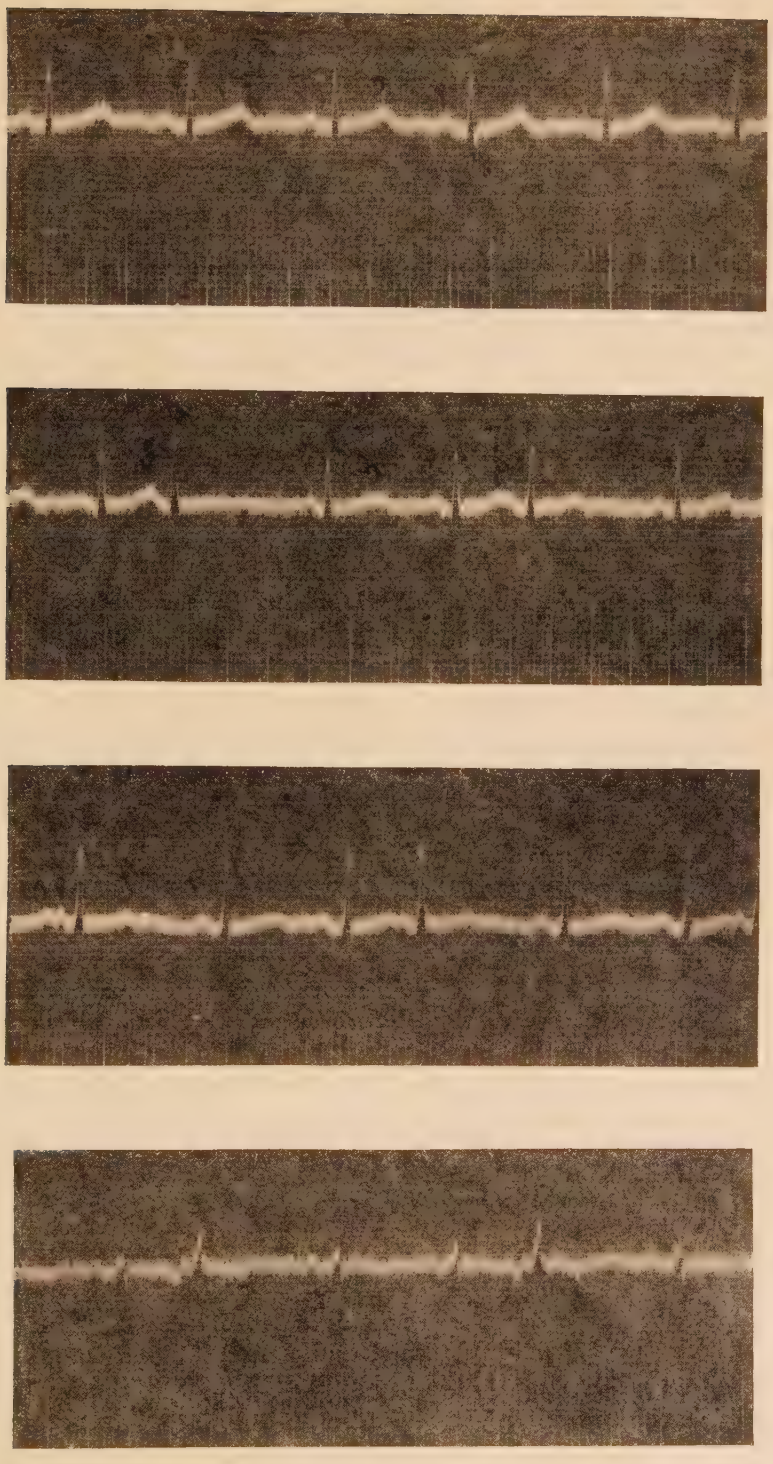


Fig. 6

(*a*) Fatal cases showing acute parenchymatous degeneration and vacuolization of the myocardium.

(*b*) Non-fatal, acute cases, showing involvement of auricle and conduction system during height of infection, with complete restoration to normal cardiac mechanism with subsidence of infection. Duration two to six weeks.

(*c*) Non-fatal chronic cases with arrhythmia and involvement of the auricle persisting and causing partial invalidism long after subsidence of acute infection. Duration twelve to seventeen months—plus.

3. Suggestion is offered that acute respiratory infections (Influenza, Streptococcus) single out early the auricle and conduction pathways of the heart.[1]

Appreciation to several members of the Hospital Staff is herewith offered, for permission to publish curves of their cases, and in particular to Miss Marguerite Collver, laboratory technician, for invaluable aid in the preparation of this material.

[1] Probably the infections affect the whole heart similarly (*cf.* microscopic studies of auricle and ventricle), but due to other factors, such as thinness of the auricular wall, presence of ganglion cells or other unknown conditions, disturbances of auricle and conduction pathways first become evident.

A CASE EXHIBITING SLOW AURICULOVENTRICULAR RHYTHM AND PAROXYSMAL TACHYCARDIA WITH UNUSUAL ABILITY TO INTERRUPT THE FAST RATE *

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AND

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Introduction. Tracings from clinical cases exhibiting auriculoventricular rhythm are comparatively rare, although the reports of Belski,[1] Cowan, Fleming and Kennedy,[2] and Hume[3] suggest that the condition is not uncommon, at least as a transient manifestation, in certain more or less acute diseases which especially attack the heart, such as diphtheria, rheumatic fever and subacute endocarditis. It is undoubtedly rare in chronic cardiac disease and is usually, but apparently not always, associated with extensive myocardial involvement. It may also be produced experimentally in normal individuals by various disturbances of the inhibitory apparatus.

Engelman[4] in 1903 first produced auriculoventricular rhythm experimentally in the frog by applying a ligature between the sinus venosus and auricle. Lohmann[5] in 1904 was the first to obtain it in the mammalian heart. Since that time a large amount of experimental work has been done, culminating in the studies of Meek and

* Cardiographic studies from the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania.

[1] Ztschr. f. klin. Med., 1909, lxvii, 67.
[2] Lancet, 1912, i, 227.
[3] Heart, 1913, No. 1, v, 25.
[4] Arch. f. Anat. u. Physiol. Phys., Abth., 1903, p. 505.
[5] Ibid., 1904, p. 431.

Eyster,[1] [2] who proved the actual auriculoventricular nodal origin of the rhythm by the method of initial negativity. These investigators, working on dogs, concluded that the inherent automaticity of the auriculoventricular node, although subject to wide individual variations, averaged about two-thirds that of the sinus node; when impulses did not arrive from above at a more rapid rate than they were being formed at the auriculoventricular node, the latter tended to assume the cardiac autonomy.

Experimentally produced auriculoventricular rhythm may be classified into two types, according to the method of production: Type I, which has been most studied, is produced by depression or abolition of automaticity at the sinus node, or interference with conduction of impulses to the auriculoventricular node. Consequently, it is a relatively slow rhythm. Type II, brought on by exaltation of automaticity of the auriculoventricular node, was first produced by Rothberger and Winterberg[3] by stimulation of the left accelerator nerve. It is therefore relatively more rapid than sinus rhythm.

The above-mentioned types of experimentally produced auriculoventricular rhythm, according to Lewis'[4] classification, are of the ectopic hemogenetic type. Most of the clinical cases are also of this type. The majority are due to depressive influences exerted above the auriculoventricular node, although some are doubtless aided in their production by the effect of accelerator influences on the node. As far as we are aware, no clinical case of the homogenetic type has been demonstrated to be due solely to acceleration of auriculoventricular stimulus production, although the work of Rothberger and Winterberg would seem to show that such a case would be theoretically possible.

The junctional paroxysmal tachycardias, although ectopic heterogenetic rhythms and consequently of fundamentally different character, are also classified as auriculoventricular rhythms. This group is rare, eight probable cases being reported. The characteristics of paroxysmal tachycardia distinguish them from homo-

[1] Heart, 1914, No. 3, v, 227. [2] Arch. Int. Med., 1916, No. 6, xviii, 775.
[3] Arch. f. d. ges. Physiol., 1910, cxxxv, 559.
[4] Quart. Jour. Med., 1913, No. 22, vi, 221.

genetic rhythms, but it has been impossible to differentiate absolutely some of the cases of junctional origin from paroxysmal auricular tachycardia with delayed conduction, as in Lewis'[1] second case. Lewis'[2] first case and Cohn's[3] case, however, appear to be clear-cut and establish the condition as an entity.

The case we have to report shows the following features of interest:

1. The length of time shifting of pacemaker back and forth between the sinus and auriculoventricular nodes was observed.
2. The variations in rate during auriculoventricular rhythm.
3. Alterations in *As–Vs* relations.
4. Attacks of paroxysmal tachycardia with unusual ability on the part of the patient to interrupt the fast rate.
5. The unusual behavior of the heart following the interruption of the tachycardia.
6. The resemblance of the tracings of the tachycardia, in a case which had previously shown auriculoventricular rhythm, to those of junctional paroxysmal tachycardia.

Report of Case.—Mrs. F. R., aged sixty-two years. Seen December 21 at Hospital of the University of Pennsylvania.

Chief Complaint. Palpitation of heart. The patient states that she has had attacks of palpitation of the heart since childhood. At that time she would get attacks of rapid heart beating after severe exertion. These attacks lasted a few minutes and disappeared quickly. She nevertheless took part in the ordinary plays of childhood. Gradually these attacks of palpitation have increased. For the past two years she has been practically invalided. The attacks begin often by clutching in the throat, which she says last two days. Occasionally this would arouse her out of her sleep, and at that time she would have sudden palpitation. This sudden palpitation makes her faint if she attempts to rise. Occasionally she has blackness before her eyes. From the very first of these very severe attacks of cardiac palpitation, the action could be controlled if she would hold her breath for a considerable length of time. When they could not be so controlled, when they ended they would end suddenly just as they began suddenly. Occasionally preceding an attack she would have dimness of vision. Sometimes they would come on after walking, sometimes, as has been said, in her sleep. She has had slight swelling of her legs. Vertigo rather constantly, and vertigo always accompanies the severe cardiac distress. She has shortness of

[1] Heart, 1910, No. 2, ii, 127.
[2] Ibid., No. 4, i, 306.
[3] Ibid., No. 2, ii, 170.

breath on the least exertion lately. Within the past six months she has been considerably worse and came to the hospital for rest. She has some aching in the region of her heart but no distinct pain. If an attack of palpitation of heart came on while she was walking she could usually reach home from a moderate distance, but with difficulty.

Physical examination shows the eyes entirely normal. There is no arcus senilis. There is slight edema of the skin over the body. Nothing abnormal noticed about the ears. There was no glandular enlargement. She had some capped teeth, but apparently the teeth in general are in good condition. Her neck and throat are normal.

Chest is normal in shape. She is spare for a woman of her general size. There is marked pulsation of the vessels of the arms and neck. Expansion of the chest is normal. Abdomen is normal in shape.

Cardiac impulse is feeble. Apex-beat is best felt just inside of the nipple line. Dulness of heart is right edge of sternum, upper border of third rib and midclavicular line. There is a loud systolic murmur over the aorta and midsternum, and also over the region of the apex. This murmur is conducted into the axilla. During this examination there is no arrhythmia. The first sound is almost totally replaced by the murmurs. Second sound is not unduly accentuated.

Lungs are entirely normal and abdominal examination is entirely normal. At this first examination her heart was beating at about fifty per minute and was perfectly regular. On January 6, 1920, she was seen in attack of tachycardia. Cardiac impulse was diffuse, but the dulness was apparently not increased. On auscultation the heart's action was regular, the murmur, which was loud during the slow action of the heart, was difficult to hear. She was asked to hold her breath, which she did, and immediately after one or two attempts of interruption of the rhythm the heart slowed down and continued while the examiner was in the room, at the rate of about fifty a minute.

All of the laboratory tests were normal.

The clinical points noticed in the case were, first, apparently the case was one of ordinary paroxysmal tachycardia in a heart which between the paroxysms acted slowly. Again there was the unusual ability for her to control the attacks of paroxysmal tachycardia by holding her breath, and the time between the first slow beats seemed to the examiner unusually long, as though some block were occurring. After about two weeks' rest in bed her heart slowed down and the patient left the hospital on January 31, 1920, very much more comfortable, and had not had an attack of tachycardia for two weeks.

She went from Philadelphia to Montrose, Pa., in a comfortable car, developed a severe distressing cough with fever and began in about a week to manifest signs of cardiac decompensation. She was seen in Montrose

with a typical attack of decompensation, heart beating about 160, dyspnea, large liver, edema of the lungs and finally death in two weeks after the beginning of this condition. No autopsy was held.

Observations on the Slow Auriculoventricular Rhythm. Tendency for the rhythm to alternate between the sinus node and the auriculoventricular node. During the entire period of four weeks, while electrocardiographic studies were being made, a constant shifting of the pacemaker back and forth between the sinus and auriculoventricular nodes was observed, except during the periods of tachycardia. Tracings show two to twenty cycles of normal rhythm, followed by transition to the slow rhythm, then abrupt change to the normal rhythm again. The periods of auriculoventricular rhythm observed varied from about thirty seconds to at least several minutes. Absolute rest and quiet favored longer periods of slow rhythm. Mild excitement, such as caused by applying electrodes, increased the frequency of periods of normal rhythm. Pressure on the vagi or ocular pressure sometimes cause shifting of the pacemaker back to the sinus node, but the results were inconstant. Once a slight cough was followed instantly by return of normal rhythm, sometimes deep breathing produced the same result. Under varying amounts of atropin,[1] the tendency for the pacemaker to shift spontaneously was not abolished.

Variations in Rate During Auriculoventricular Rhythm. The transition to auriculoventricular rhythm was sometimes preceded by a slowing of the sinus rhythm (Fig. 2 *A* and 2 *B*) sometimes came on following an auriculoextrasystole (Fig. 1 *A*), but frequently occured abruptly (Fig. 1 *B*) without preceding slowing of sinus rhythm or extrasystole. As a rule, after two or three cycles, with increasing *R-R* intervals, the rate reached 30 to 45, and with minor variations tended to increase gradually until eventually it became fairly steady around 50 to 60, until the onset of the next period of sinus rhythm.

Owing to the spontaneous variations in rhythm the case was not favorable for study of changes due to vagal influences. Pressure

[1] Atropin sulphate was administered by mouth, gr. $\frac{1}{100}$ q. i. d. for one day and t. i. d. the next four days. All statements in respect of atropin effect refer to observations made during this period.

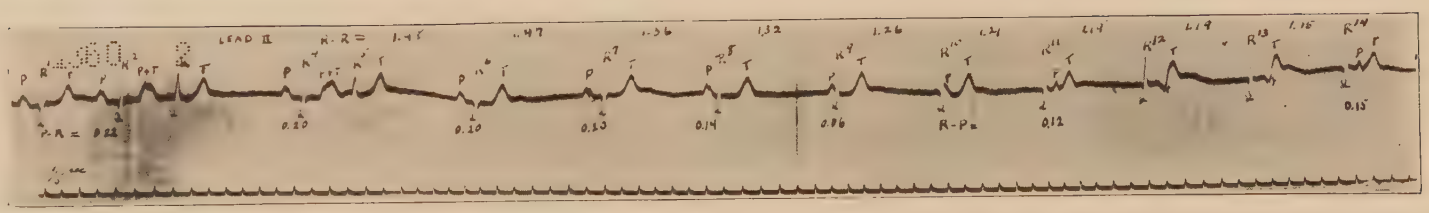

Fig. 1 A.—Lead II. Taken January 2, 1920. First two cycles end a short period of sinus rhythm, followed by extrasystole with delayed conduction. The beginning of auriculoventricular rhythm interrupted by another extrasystole. Gradual development of *R–P* sequence, also gradual acceleration of rate. The patient had received tinct. digitalis ℳx by mouth the evening before and again on the morning this tracing was made.

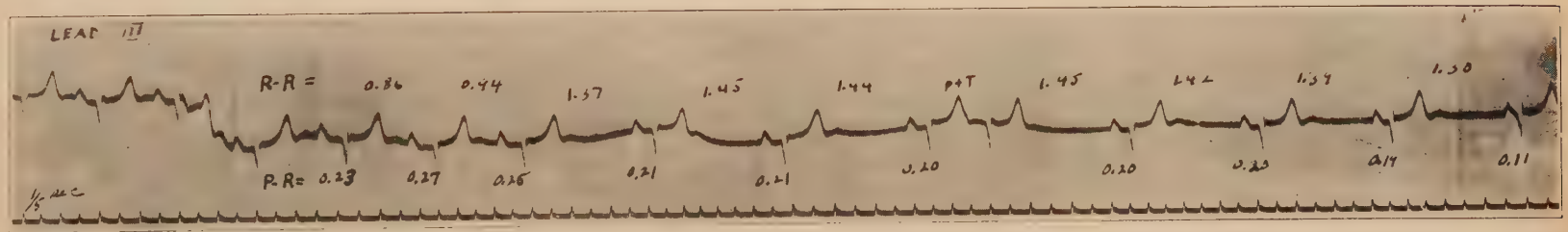

Fig. 1 B.—Lead III. Taken immediately after Fig. 1 A. First three cycles end a period of normal rhythm showing depressed conductivity. Abrupt onset of auriculoventricular rhythm. Gradually decreasing *P R* intervals. Tendency toward acceleration of rate during auriculoventricular rhythm.

on the neck, ocular pressure and deep breathing produced no appreciable change except in so far as they sometimes initiated sinus rhythm. The atropin administration also was without apparent effect on the rate of the auriculoventricular rhythm.

The Relations of Auricular Systole to Ventricular Systole. A slight depression of conductivity, which was not abolished by atropin, was noted in all the tracings, and at no time during sinus rhythm was the *P–R* interval shorter than 0.2 seconds. In Fig. 1 it varies but reaches a maximum of 0.27 second. In connection with the onset of auriculoventricular rhythm the *P–R* interval shows an immediate slight decrease. In general, after maintaining this relation for a few cycles, *P* gradually approaches *R* until it becomes lost in the *Q R S* group, sometimes emerging again to the left for a few cycles (Fig. 2 *B*, last cycle). The changes in *P–R* intervals occur usually in relation to changes in rate, the intervals decreasing toward zero as the rate increases. However, this relation is not constantly observed. Fig. 1 *A* shows *R–P* intervals, and was the only tracing in which they were obtained.

Neither pressure on the vagi, ocular pressure, deep breathing nor the administration of atropin produced any appreciable changes in the relation of *P–R*.

Observations on the Tachycardia and the Interruptions Produced by the Patient. The tracing shown in Fig. 3 was taken during one of the paroxysms of tachycardia. The rate was about 135, the rhythm regular and the ventricular complexes, with minor differences in Lead II, are similar to those occurring during sinus rhythm, except for the presence of the *P* wave between the *Q R S* group and the *T* wave.

The patient for years had been able to inhibit the tachycardia temporarily, and occasionally terminate an attack by taking a deep breath and holding it. This maneuver was not always successful, but frequently a cycle of events, of which Fig. 4 shows an example, occurred. After the breath was held from ten to fifteen seconds the tachycardia would terminate suddenly, sometimes with a moderately long pause followed by an isolated contraction, then an extremely long pause of from four to five seconds (Fig. 5 *A*), while sometimes the longest pause would occur immediately after the interruption of

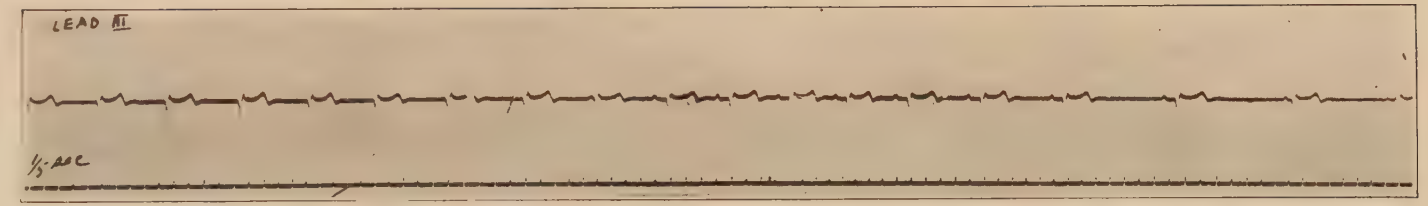

Fig. 2 A.—Lead III. Taken January 24, 1920. Auriculoventricular rhythm, rate about 60. No *P* wave visible. Spontaneous short period of sinus rhythm. Only slight conductivity defect; the *P-R* interval does not exceed 0.2 second. Slow auriculoventricular rhythm following sinus rhythm. Patient had received atropin sulphate gr. $\frac{1}{100}$ eight times in the preceding forty-eight hours and showed physiological effects.

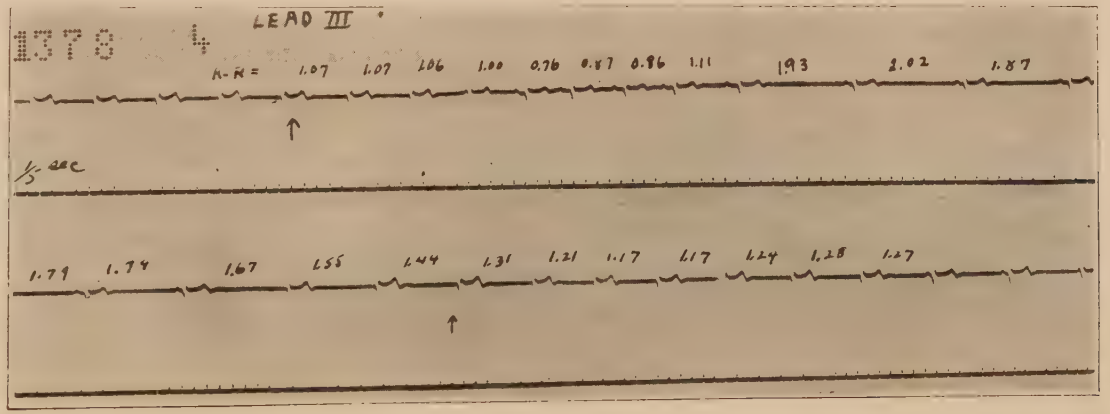

Fig. 2 B.—Lead III. Taken immediately after 2 A. Deep breath at point indicated by first arrow, held until point indicated by second arrow. Alteration in ventricular complex while breath was held. This tracing shows the typical variations in rate during the auriculoventricular rhythm, and their relations to a period of sinus rhythm.

the tachycardia (Fig. 4). Following the long pause, contractions of supraventricular origin but showing no evidence of *P* wave, occurred irregularly with single contractions or short runs of sinus origin interspersed. When the period of interruption lasted longer a fairly regular slow auriculoventricular rhythm became established, interrupted by short runs of sinus rhythm, similar in every way to the behavior of the heart observed apart from the paroxysms of tachycardia.

The position of the *P* wave with reference to the ventricular complex during offset and onset, and during the period of interruption is of some interest. Figs. 5 *A* and 5 *B* show no evidence of auricular activity within the last ventricular complex before the offset. In Fig. 5 *A* the first cycle after the offset has a *P–R* interval of 0.38 second. In Fig. 4 during the interruption the longest *P–R* interval, observed in cycles of sinus origin, is 0.28 second. The tachycardia is initiated again by a cycle with a *P–R* interval of 0.37 second.

COMMENT. *The Slow Rhythm.* While frequent alternations of the pacemaker back and forth between the sinus and auricular nodes has been observed in several cases, usually, as in those reported by Lewis[1] and Laslett,[2] the rates of stimulus production in the two centers are fairly close, so that Laslett's suggestion of variations in vagal tone, as the determining factor in the shift, might well apply. In our case attempts at stimulation of the inhibitory apparatus appeared to have some effect, but not a constant one, in bringing about a few cycles of sinus rhythm, or at least hastening the recurrence of such a period; however, the sinus rhythm would not persist whether stimulation be continued or not. On the other hand attempts to remove inhibitory control by atropin did not abolish the shifting back and forth of the pacemaker. The very slow rate following the sinus rhythm revealed the fact that the ability to produce stimuli in the sinus node must have been almost if not completely exhausted temporarily, and despite any nervous influences that could be brought to bear, required at least some rest to bring about a restoration of the function. The main effect of

[1] Quart. Jour. Med., 1913, No. 22, vi, 221. [2] Heart, 1910, No. 1, vi, 170.

nervous influences was apparently to alter the length of the period before the node became able to discharge impulses again.

Changes in relation of auricular systole to ventricular systole during auriculoventricular rhythm have been studied experimentally

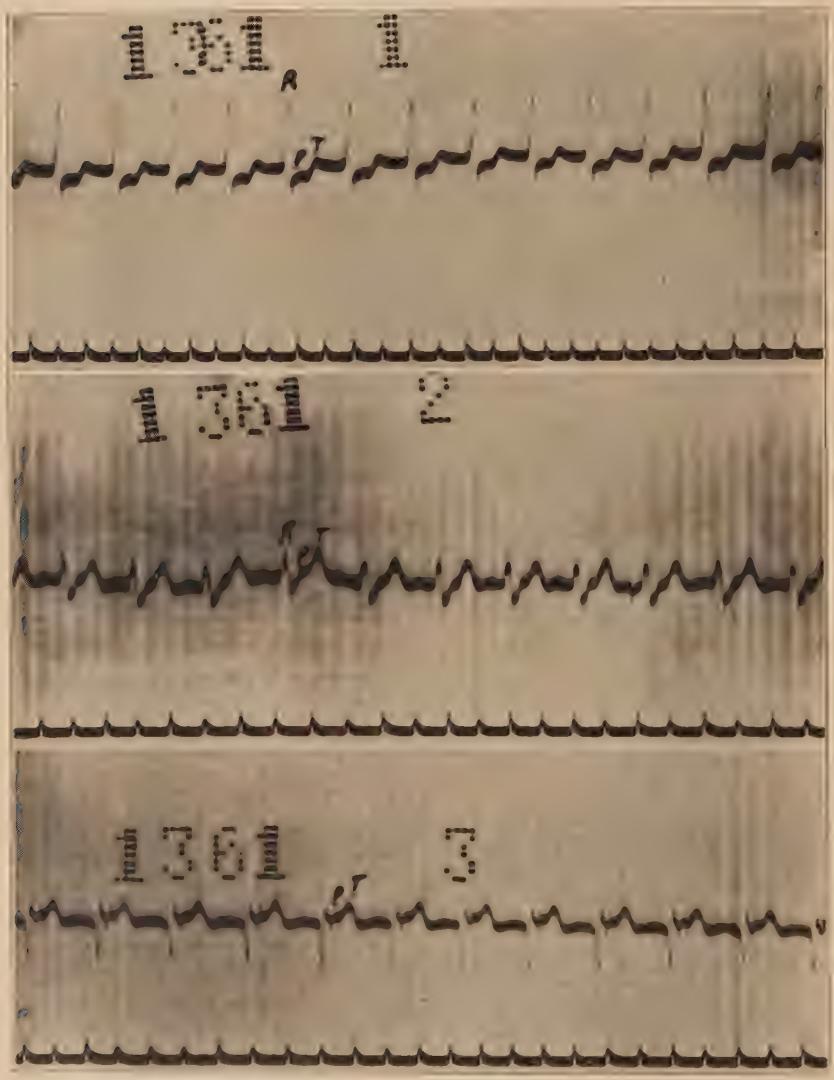

FIG. 3.—Taken January 3, 1920. Shortly after the onset of the tachycardia. *P* wave between *Q R S* complex and *T* wave in all three leads.

by several observers. Hering[1] suggested that they were due to migration of the pacemaker. Zahn[2] and Meek and Eyster[3] demonstrated that migration of the pacemaker was accompanied by change in *As–Vs* intervals. According to the latter, coronary sinus rhythm was accompanied by only slight shortening of *As–Vs* time, but when the impulse arose in the lower or ventricular portion of the node the ventricles might contract even before the auricles. Lewis, White, and Meakins[4] have shown that reversed block might also account for changes in *As–Vs* relations during auriculoventricular rhythm, not only to the extent of producing *Vs–As* intervals but to failure of transmission of impulse back to the auricles. White,[5] in his clinical case was able to increase *R–P* intervals by vagal stimulation and by digitalis and to decrease the intervals lengthened by digitalis through the administration of atropin. These effects were produced presumably by modifying reversed conduction. In those clinical cases without depression of conductivity, spontaneously changing *As–Vs* relations are probably dependent largely if not wholly on migration of the pacemaker. Weil[6] ascribed the alterations in *P–R* intervals observed in his tracings to this factor.

In our case the facts suggest that both migration of the pacemaker and depressed conductivity are involved in the changing *As–Vs* relations as seen in Figs. 1 *A* and 1 *B*. Explanation on the basis of independent auricular and ventricular contractions falling near each other is easily excluded, for even if it were granted that both auricles and ventricles might be contracting at the same slow rate it would be unreasonable to expect them to maintain their relations in view of the irregularities in rhythm that occur.

P–R intervals up to 0.27 second during the sinus rhythm evidence well-marked depression of conductivity. The fact that *P–R* intervals during the early cycles of auriculoventricular rhythm may still be 0.20–0.21 second (Fig. 1 *A* and 1 *B*) demonstrates that the principal defect in conductivity lies beyond the point of formation of impulses, consequently a slight forward block is evident. But even complete recovery of conductivity could not account for the

[1] Arch. f. d. ges. Physiol., 1910, cxxxvi, 446.
[2] Ibid., 1913, cli, 247.
[3] Heart, 1914, No. 3, v, 227.
[4] Heart, 1914, No. 3, v, 289.
[5] Arch. Int. Med., 1915, No. 4, xvi, 517.
[6] Deutsch. Arch. f. klin. Med., 1914, cxvi, 486.

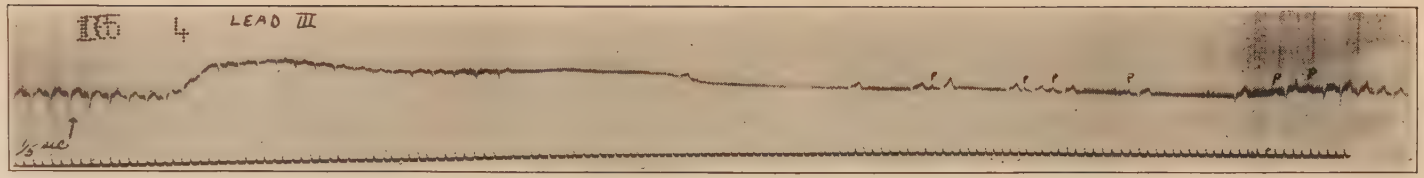

FIG. 4.—Lead III. Taken January 7, 1920. Shows sequence of events, following interruption of fast rhythm. Deep breath taken at point indicated by arrow. Held until patient was aware of changed rhythm. Long pause of 4.5 seconds, followed by ventricular escape. No regular rhythm established during the interruption. Long *P–R* interval at onset of tachycardia.

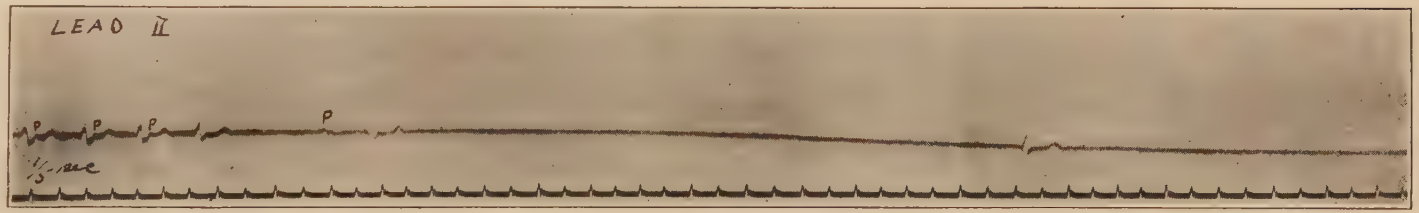

FIG. 5 A.—Lead II. Taken January 5, 1920. Interruption of tachycardia. Last ventricular complex before offset does not show deformity due to *P* wave. Next contraction shows long *P–R* interval. The long pause lasts 4.9 seconds.

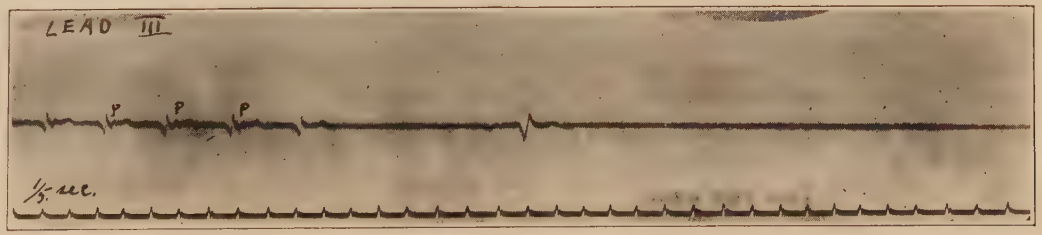

FIG. 5 B.—Lead III. Taken immediately after 5 A. Interruption of tachycardia. Last ventricular complex does not show deformity due to *P* wave.

development of *R–P* intervals. On the other hand, numerous tracings taken later, when conductivity was improved, as in Figs. 2 *A* and 2 *B*, show not only shorter *P–R* intervals at the beginning of the auriculoventricular rhythm but no *R–P* relations at all. Consequently the only explanation that seems adequate to account for the facts observed is the assumption that the region of the defect of conductivity is within the auriculoventricular node; at the beginning of auricular rhythm it lies beyond the pacemaker and slight forward block is present; but by the migration of the pacemaker to lower levels of the node it is passed and slight reversed block occurs.

The Tachycardia. The tracings shown in Fig. 3 admit of two possible interpretations: (1) Paroxysmal junctional tachycardia with *R–P* intervals or (2) paroxysmal auricular tachycardia with delayed conduction. The explanation is furnished by the tracings showing interruption and onset of the rhythm (Figs. 4, 5 *A* and 5 *B*). The last ventricular complex before offset shows no *P* wave as it would if the rhythm were of junctional origin, while the onset is initiated by a cycle with a *P–R* interval of 0.37 second, demonstrating that conduction is delayed sufficiently for the auricular systole of a particular cycle to fall within the ventricular systole of the preceding cycle during the tachycardia.

The fact that conduction is so much more delayed during the tachycardia than occurred with sinus rhythm is not to be explained in this case on the basis of depression of conduction due to more frequent transmission of impulses. The first cycle of tachycardia shows the same marked delay in comparison with the contractions of sinus origin that occur just before it (Fig. 4). The same delayed conduction is seen when auricular extrasystoles interrupt either sinus or auriculoventricular rhythm. (Figs. 1 *A* and 1 *B*). The probable explanation is furnished by the work of Eyster and Meek,[7] who show that conduction from the sinus to the auriculoventricular node occurs normally not by spreading of the impulse through the mass of auricular tissue but by specialized conduction paths; while conduction by the auricle may be accomplished it is difficult and prolonged. Consequently, whether ectopic auricular impulses are carried to the auriculoventricular node either through the mass of auricular tissue or back to the sinus node and thence through the

sinoventricular conduction paths the *As–Vs* time might be prolonged.

The mechanism by which the patient was able to interrupt the tachycardia was not clear. It has long been known that stimulation of the inhibitory apparatus may interrupt a paroxysm of tachycardia, but as shown in the cases studied by Cohn and Fraser[1] this usually occurs promptly. We were unable to initiate the change by pressure on either vagus or by ocular pressure. Carter and Wedd[2] exhibit tracings in which the tachycardia was thought to be interrupted by the aid of some voluntary effort on the part of the subject. In our case the fact that holding the breath for at least ten to fifteen seconds was necessary, raises the question as to whether slight asphyxial influences might temporarily depress the irritability of the ectopic focus in a heart with evident advanced myocardial disease and doubtless a precarious blood supply.

The unusual behavior of the heart following the interruption of the tachycardia—which, so far as we are aware, is unique—was probably due, in part at least, to the easy exhaustion of stimulus production in the sinus node, which was pointed out above as the principal factor concerned in the shifting back and forth of the pacemaker during the periods of slow rhythm. Whether still further depression of the sinus node was caused by the same mechanism that depressed the irritable focus in the auricle could not be determined. Evidently, however, the automaticity of the auriculoventricular node was markedly disturbed and required time for its recovery so that regular auriculoventricular rhythm could be established only during the longer periods of interruption of the tachycardia.

SUMMARY. A case is reported with a history of attacks of paroxysmal tachycardia occurring over a period of more than forty years; an ability to interrupt the fast rhythm with temporary cessation of cardiac activity; periods of slow rhythm with interspersed short runs of about the normal rate; abundant clinical evidences of myocardial disease and with slight decompensation.

The electrocardiographic tracings showed left ventricular preponderance, depressed conductivity, periods of sinus rhythm alter-

[1] Heart, 1913, No. 1, v, 93.

[2] Arch. Int. Med., 1918, No. 5, xxii, 571.

nating with auriculoventricular rhythm, and auricular paroxysmal tachycardia.

Observations were made in respect of the alternations of the pacemaker between the sinus and auriculoventricular nodes, variations in rate, relations of auricular systole to ventricular systole; the significance of these phenomena was disucssed.

The paroxysmal tachycardia was determined as auricular in origin by analysis of curves of offset and onset. The method by which the patient obtained interruption of the tachycardia was described, and an attempt made to evaluate the factors responsible for the behavior of the heart during the period of interruption.

NON-DIALYZABLE BILE PIGMENT IN PLASMA

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In making a more or less extensive investigation of the various clinical types of jaundice, I attempted several years ago to separate bile salts from the blood by dialyzing oxalate plasma through collodion membranes into water. I observed that in some instances bile pigment could be dialyzed readily, while from other specimens, even though plenty of bile pigment was present, none of it would dialyze.

At a previous meeting of this Association, I reported[1] that I had found both dialyzable and non-dialyzable bile pigment in blood—non-dialyzable alone in the milder grades of jaundice, and both dialyzable and non-dialyzable in the more severe grades of jaundice. I also reported that, when dialyzable pigment was present in the blood, bile pigment was usually found in the urine; and when no pigment could be dialyzed from the blood, none would be found in the urine. There have been very few exceptions to the rule that bile pigment of the blood diffuses through collodion membrane whenever it goes through the kidney.

This method of study has disclosed many cases of acholuric jaundice, some so faintly jaundiced that a chemical test of the plasma with nitric acid was the only evidence of jaundice, others so very yellow that the absence of choluria demanded explanation. In a very few of the latter cases, impairment of kidney function could be admitted as a possible cause. In others, where no defect in kidney function could be found, it was assumed that something

[1] Blankenhorn, M. A.: Distribution of Bile in Certain Types of Jaundice, Arch. Int. Med., 1918, xxi, 282.

peculiar to the conditions of cholemia determined the retention of pigment. This report, then, deals with the nature of such bile pigment as could not be dialyzed from the blood plasma and did not appear in the urine. Forty specimens were investigated. They were in every case oxalate plasma, free from hemolysis, obtained from patients that were admitted to the medical wards for study and treatment. In every instance the urine was examined for bile and an inspection of the skin and scleræ made for jaundice. Also jaundiced specimens of plasma were fabricated in the laboratory by adding various amounts of fresh gall-bladder bile to freshly obtained oxalate plasma. It was found that, when sufficient gall-bladder bile was added to give the plasma a deep yellow stain, the plasma when dialyzed in water would give up only a part of the bile pigment, and that prolonged dialysis in running water would not completely decolorize the plasma to its original condition. The amount of pigment thus remaining undialyzable is quite variable. It was also found that, when colorless plasma was placed within the collodion sac with a dilute aqueous solution of gall-bladder bile surrounding the sac, the bile pigment would penetrate the membrane and stain the plasma, but subsequently could not be completely removed by dialysis.

Jaundiced plasma obtained from patients was dialyzed into small amounts of water to determine the presence of any dialyzable pigment, and if any was found the plasma was then dialyzed for twenty-four hours in running water, the non-dialyzable residue being preserved. In no instance was it possible to completely decolorize plasma by dialysis. But there was quite a wide variation in the amount of undialyzable residue in different specimens.

It was found that, when the proteins were removed from plasma by coagulation with heat, the coagulated proteins were stained yellow or yellowish green, and that when only non-dialyzable pigment was present, coagulation of the plasma and filtration removed all of the color. In plasma that contained dialyzable as well as non-dialyzable pigment, coagulation by heat and filtration did not remove all color. However, after such specimens were dialyzed with running water for twenty-four hours, thus removing all dialyzable pigment, and then coagulated with heat, filtrating would remove

all of the color. It was then apparent that non-dialyzable bile pigment is associated with the protein of the plasma. When the protein of the plasma was removed by salting out and then precipitated, the precipitate was found to be yellow or green, depending on the amount of pigment present. After complete precipitation by salting out, the filtrate would be entirely colorless and give no biuret reaction. When proteins were salted out fractionally[1] by ammonium sulfate, all three elements—euglobulin, pseudo-globulin, and serum albumin—were found to be pigmented.

Heat-coagulated proteins can be washed with water, dilute acids and alkalies without losing any of their pigment. When extracted with alcohol, the pigment is quickly and entirely removed, and can then be identified as bile pigment by the various color tests. No pigment can be removed by prolonged extraction with ether or petroleum ether. Strong acids or alkalies may dissolve the coagulated proteins or destroy their added pigment, but they do not extract the pigment unchanged as does alcohol.

Precipitated proteins which are stained by bile pigments behave in the same manner to solvents—*i. e.*, they give up their bile pigment only to alcohol, and not to dilute acids and alkalies or to ether and petroleum ether.

When heat-coagulated proteins or precipitated proteins are acted upon by pepsin, they go into solution readily and still retain their yellow or green color. When dialyzed in this form, a certain amount of bile pigment will dialyze, but not until some of the protein—probably peptone—is dialyzed; that is, the undigested protein together with its pigment does not dialyze at all, but when acted upon by proteolytic enzymes, metaproteins are formed which are more diffusible but which apparently retain their stain of bile pigment. In no instance was any staining substance found in the plasma which could not be coagulated out by heat and precipitated by salting out. It would appear, therefore, that non-dialyzable bile pigment in the blood is combined with the proteins by absorption—like a colloid stained by a dye.

In a previous report I offered the suggestion that acholuric jaundice might be explained by retention of bile pigments in the

[1] Marawitz, P.: Handb. der Biochem. des Men. u. d. Thiere, Part II, ii, 79.

blood, but that such pigment was essentially different from that which was readily dialyzed. I was led to believe this by noticing that in obstructive jaundice, which is the simplest type of jaundice, there is very little non-dialyzable pigment in the blood; but in diseases of the liver, particularly of long standing, there is usually a large amount of non-dialyzable pigment. This suggested that the formation of non-obstructive jaundice was not simply a process of pouring bile pigment into the blood stream, and that the pigment by its elaboration in the liver was of a different nature from pigment found in obstructive jaundice. However, on further study of the various types of acholuric jaundice, this appearance of a different pigment was not substantiated. It was noted however, that most of the cases of acholuric jaundice have been jaundiced for a long time. When severely jaundiced for a long time, there is a large amount of non-dialyzable bile pigment; when mildly jaundiced for a long time, there is a less degree. It is quite probable that the retention of bile pigment can be explained as a staining of the blood proteins, and that the degree of stain varies according to the concentration of the stain and the length of time that the plasma is exposed to the stain.

THE PURIFICATION AND CONCENTRATION OF ANTIGENS FOR COMPLEMENT FIXATION BY METHODS OF DIALYSIS, ADSORPTION AND EXTRACTION

By AUGUSTUS B. WADSWORTH, M.D.

AND

FRANK MALTANER

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The complement-fixation test of Bordet and Gengou, with bacterial antigens on the serum of highly immunized animals, has been of value in the identification of bacterial species, but it has never been a practical aid in the diagnosis or prognosis of bacterial infection in man. Although the antigens which have been prepared from syphilitic tissue and even from certain normal tissues have proved to be of the greatest value in the diagnosis of syphilis, none of the antigens which have been prepared from pure cultures of the spirochete isolated from syphilitic antigens has been reliable. On the contrary they apparently lack reactive capacities that are characteristic of the disease. Thus the nature of the complement-fixation reaction of Wassermann is quite obscure.

The so-called "anti-complementary" or "non-specific" properties of the antigens which have been prepared from the pure cultures of the incitants of the infection have made it difficult or impossible to standardize the test so that the characteristic reactions with the blood serum from cases of infection could be detected or studied to determine the diagnostic or prognostic value.

Prior to his work on syphilis, Wassermann studied the complement-fixation reaction in tuberculosis but failed to prepare satisfactory antigens from the tubercle bacilli. Recently a number of investigators have reported diagnostic reactions in so many cases

of tuberculosis that there can be no question that it is possible to prepare antigens from the tubercle bacillus, and in certain stages of the disease the blood serum gives positive reactions with them; but it has not been possible to standardize the test so it is reliable in the diagnosis of the disease or in the study of the development of immune reactions in different stages of the disease.

We began our studies in 1917, with the primary object in view of so standardizing the preparation of the antigens that it would be possible, first, to study the development of immune reactions in experimental infection in animals and later, to determine the diagnostic value of the test in human cases of the disease.

New methods of dialysis and absorption were used in the preparation of the antigens by which the antigenic substances were greatly purified and concentrated. The purpose of this preliminary paper is to record these new methods.

The work may be divided into three sections: (1) deals with the preparation of standard immune serums; (2) comprises the painstaking investigation of the antigenic properties of different fractions of the culture to determine which of them should be selected for the clinical study of the diagnostic value of the test or used for further research with methods of purification or concentration; (3) includes these new methods.

All the cultures were made in a beef infusion broth containing 1 per cent. of Fairchild's peptone, 0.5 per cent. salt, 0.5 per cent. glycerin and titrated to react 0.5 per cent. acid to phenolphthalein. The medium was sterilized fractionally in the Arnold sterilizer. Mass cultures were grown in quart or pint Blake bottles containing 100 c.c. of media at a temperature of 37.5° C. The growth was taken for study in some cultures as soon as the pellicle had become fully developed and in others as soon as growth ceased. After filtration the residue of tubercle bacilli was washed with saline solution and dried partly with blotting-paper. They were then desiccated over concentrated sulphuric acid or calcium chloride. The bacilli were pulverized in a ball mill for about ten days. This material was then extracted with different substances, such as carbon disulphide, ether, chloroform and carbon tetrachloride until all the fats and waxes had been removed. Various antigens were prepared from these extractions and the fat-free residue was then extracted with distilled water, saturated salt solution, sodium hydrate, hydrochloric acid and glycerin.

The preparation of standard immune serums with these three cultures was a prolonged investigation of experimental infection and immunization of a large number of animals which was successfully carried on by Miss B. Johnston and will be recorded more fully in another paper. It involved not only the testing of the inoculated animals at frequent intervals but also a study of the precipitation of the globulin fraction of serum. Finally, sufficiently active immune serums were obtained from horses with all three strains of the tubercle bacillus to give complete fixation of complement with the antigens which were arbitrarily selected to start this work. One bleeding of the horses gave such a large quantity of serum that titration of the comparative value of all antigens could easily be made.

The results of the experiments in which the different fractions of the culture were tested with the standard immune serums must also be briefly summarized. The preparation of antigens by extraction of tuberculous tissues was unsatisfactory. The culture filtrates were so anti-complementary that they could rarely be used. Of all the extracts of the tubercle bacillus which have as yet been tested in our experiments, glycerin and especially distilled water produced the most active antigens. These active antigens were selected for further study by methods of adsorption.

Animal charcoal and globulin (horse serum) were used to absorb the substances possessing antigenic action. When animal charcoal was added, the active antigens lost their antigenic properties and it has been as yet impossible to recover from the animal charcoal any of the antigenic properties. When globulin was added and precipitated with CO_2 and the precipitate extracted with alcohol the substances possessing antigenic action with tuberculous immune serum were absorbed and recovered in a greatly purified and concentrated condition. The so-called anti-complementary action which all the original antigens possessed could not be detected in the lowest dilutions of the alcoholic extract (1 to 10) which could be used. The lytic action which some of the original antigens possessed also disappeared.

The technic that was used may be briefly summarized as follows:

The original antigen was dialyzed and horse serum, 1 part to 20 of antigen, was added and allowed to stand in the incubator half an hour. The globulin was then precipitated by passing purified CO_2 gas free from HCl through the mixture for one-half an hour at 37° C. The globulin precipitate was collected, and by shaking it with alcohol the antigenic substances were extracted. The alcoholic extract was concentrated in a vacuum.

All the titrations were made in quantities of one-tenth the original Wassermann test.

An extremely interesting observation was made when the culture filtrates were studied. In order to eliminate all the dialyzable substances which prevent the adsorption of the antigenic substances by globulin, the culture filtrates were dialyzed for at least five days. Tests of the antigenic properties at different stages of the process revealed the fact that after dialysis the filtrate became active as an antigen, and lost its anti-complementary action. After precipitation with CO_2 and extraction of the globulin precipitate much more active antigens were obtained. The most active antigens, however, were those obtained by this method from the distilled water extracts of the tubercle bacillus.

To illustrate the degree of concentration and purification: broth filtrates which were so anti-complimentary that they gave no "specific" fixation, after dialysis were not anti-complementary and .02 c.c. gave one unit of antigen; that is, complete fixation with the standard quantity of immune serum—two units as determined by a previous titration with one of the crude antigens which were used to standardize the immune serums. After adsorption and concentration .0003 c.c. gave a unit of antigen. The aqueous extract antigens were anti-complementary in doses of approximately .05 to .01 c.c. The results of purification and concentration of these antigens are even more striking. Before dialysis .003 c.c. of one of them contained one unit of antigen, after dialysis it was no longer anti-complementary; but owing to the increase in volume during dialysis, .005 c.c. contained one unit of antigen. After concentration .00015 c.c. contained one unit. Expressed in terms of antigenic units in each cubic centimeter this is an increase from 333 to 6666.

The results of preliminary experiments with antigens which are used in the diagnosis of syphilis indicate that these antigenic properties may also similarly be purified and concentrated. These new methods thus open up possibilities for more precise study of many phases of infection and immunity than has hitherto been possible.

DISCUSSION

Dr. Paul Lewis, of Philadelphia, said that he would like to ask whether Dr. Wadsworth had found any indication as to whether alcoholic extract comprised the whole of the antigenic character of the tubercle bacillus, or was there anything in the residue which was injected. There was a difference between antigens of bacterial suspension and the alcohol extract. Four hours' primary incubation was necessary to develop the full antigenic value of the bacterial suspension. Was this the case with the alcoholic extractive? He thought it usually developed its value in half an hour.

Dr. Augustus Wadsworth, of Albany (closing), said that their original plan was laid out to determine that point and others, but he did not feel as yet that they understood the full significance of this work. They were just at the beginning of the investigation as regards physical conditions and further facts might clear up that question. The filtrate after dialyzing became active without any extraction. Simple removal of the dialyzable factor removed that anti-complementary power. In the tests made by them the complement, treated that way, acted in a similarly specific manner to the antigen prepared from alcoholic extract after absorption from globulin. By diluting alcoholic extract 1 to 10, the action was similar to the action of the filtrate.

THE ROLE OF THE ELECTROCARDIOGRAM IN PROGNOSIS: A STUDY LIMITED TO HEARTS UNDER SINUS CONTROL AND CONTRACTING AT AN APPROXIMATELY NORMAL RATE

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AND
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Aid in prognosis has long been sought through an interpretation of graphic records of heart-action currents. The value of a correct diagnosis as a basis for prognosis cannot be questioned. The nature of an arrhythmia can be demonstrated through a study of electrocardiographic curves. Yet the profession has been slow to avail itself of laboratory aids in the diagnosis and prognosis of irregularly beating hearts. Physicians have been even less liable to seek information in regard to those patients whose heart action is regular, especially if the heart-rate is not accelerated. Yet even in the latter group of hearts the electrocardiogram may furnish important information as to the state of the myocardium, information which may be essential to the forming of a correct prognosis. The object of the present paper is to attempt to assess the prognostic value of information derived from the study of electrocardiograms obtained from patients whose hearts were beating under the domination of the normal pacemaker and at a rate which was approximately normal.

Our records were collected in a general hospital in a large industrial city. The patients who were electrocardiographed were nearly all adults; the age incidence varied but the average was probably less high than would be found in many hospitals of the strictly charitable type. Patients were referred to the heart station from various departments in the hospital and by outside physicians, the

services of the heart station being equally available to all. The following table indicates the source of the clinical material:

Total number of patients examined	780	
Medical service	480	61.5 per cent.
Gynecologic service	67	8.5 "
Dispensaries	49	6.2 "
Psychopathic service	29	3.7 "
Surgical service	11	1.4 "
Nose and throat service	4	0.5 "
Pediatric service	2	0.25 "
Genito-urinary service	2	0.25 "
Obstetric service	0	0.0 "
Unclassified as to service	80	10.0 "
Outside physicians	56	7.1 "
Number of cases excluded on account of ectopic origin of heart-beat or of rapid rate	220	
Available for purpose of present study	560	

The following abnormalities of the electrocardiogram have been considered.

1. Such distortions of the primary ventricular complex as are usually associated with conduction defects below the bifurcation of the main bundle.

2. Decreased amplitude of primary ventricular deflection as existing in the absence of other marked distortion of the electrocardiogram.

3. Prolonged P–R interval.

4. Invert T_1.

5. Alternation of heart action currents or of the strength of pulse-waves as registered upon the electrocardiographic plate by means of a special device.

We fully recognize the limitations imposed upon us by the nature of the material studied: in spite of these limitations we believe that the study has not been entirely fruitless. The method carried with it at least one definite advantage—the elimination of the element of expectant attention.

I. Distortions of the primary ventricular complex have recently been the subject of careful study.

Oppenheimer and Rothschild[1] have called attention to the frequent association of certain definite peculiarities of the Q–R–S deflections with a group of clinical conditions—arteriosclerosis,

[1] Electrocardiographic Changes Associated with Myocardial Involvement, Jour. Am. Med. Assn., August 11, 1917, lxix, 429.

coronary artery disease, syphilis—which are liable to be accompanied by degenerative changes in the heart muscle. These authors made postmortem studies of the hearts of 14 patients from whom electrocardiograms showing distortion of Q–R–S deflections of a special type had been obtained during life. Disseminated sclerosis which predominated in the endocardial and subendocardial layers was found in all but one; the prognosis in the presence of the described distortion of the electrocardiogram was believed to be grave.

The electrocardiogram which these authors believed associated characteristically with this type of myocardial involvement (which results in "disturbed intraventricular conduction") is described as follows:

1. Abnormal prolongation of the time interval of the Q–R–S group beyond the normal limit of 0.1 second.
2. Notching of the R wave.
3. Occasional low amplitude of the waves in all leads.
4. Absence of the typical diaphasic curves, with large T_1 waves, as found in experimental branch bundle block.

Carter[2] concludes that "the presence of a predominant sclerosis of the terminal arborizations of the Purkinje system gives rise to electrocardiographic curves of low amplitude associated with a bizarre ventricular complex of a definite type. Curves of large amplitude, essentially diphasic, may justly be regarded from experimental evidence available, as indicative of a definite totally obstructive temporary or permanent lesion of one of the branches of the atrioventricular bundle. The presence of curves of low amplitude, so characteristic of a diffuse sclerosis, did not, however, preclude the existence of definitely localized focal lesions involving the main stem and its branches."

Robinson,[3] while accepting the conclusions of Oppenheimer and Rothschild[1] as applicable to a group of cases, has shown that a like distortion of the electrocardiogram may occur occasionally as an expression of what he believes to be temporary functional fatigue.

[2] Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations Arch. Int. Med., September, 1918, xxii, 331.

[3] Significance of Abnormalities in the Form of the Electrocardiogram, Arch. Int. Med., October, 1919, xxiv, 422.

Willius[4] states that arborization block is now generally accepted to indicate disease of the subendocardial myocardium and evidences serious functional cardiac disturbance.

Robinson's hypothesis added to the conclusions of Carter seems to be a fair summary of the present knowledge of block below the bundle of His.

A study of our records has convinced us that it is occasionally impossible to classify distortion of *Q–R–S* by the criteria of Oppenheimer and Rothschild.[1] Borderline records occur in which it is only possible to assign the block to a point below the main stem of the bundle. Furthermore, one cannot always prove that the block arises as the result of histologic lesion. Thus we have been unable to exclude the fatigue element in several of our cases, since some of our patients have presented themselves for examination but once. However, in no case have we noted a return to normal after the distortion of *Q–R–S*.

Our material consists of records of 19 patients, or a total of 3.4 per cent. of the patients with sinus rhythm. Sixty per cent. of the patients were males. The average age incidence was fifty-seven; the youngest patient was thirty-five years old. Most of the patients presented the clinical picture of cardio-renal-vascular disease. Syphilis is conspicuous by its absence. In only one case was a positive blood Wassermann obtained, this patient having an aortic insufficiency. In 10 cases the Wassermann was negative, as were history and evidence gained by physical examination. No Wassermanns were taken on any of the 8 remaining patients. In none of these was a clinical diagnosis of syphilis made, and in at least 2 of the 8 it is probable that the disease can be almost definitely excluded.

Measurement of serial plates showed that the width of the *Q–R–S* interval varied from time to time, as between 0.10 and 0.14 in one patient and 0.16 and 0.20 in another. However, widening, having once been established in a given case, the *Q–R–S* interval subsequently was never found to decrease below 0.1. The persistence of a given form of distortion, as established by an individual, has been striking at times. The following case is reported as illustrative:

[4] Arborization Block, Arch. Int. Med., April, 1919, xxiii, 431.

W. H., male, aged seventy-three years. Admitted November 20, 1915, complaining of dizziness, weakness, dyspnea and swelling of the feet. The diagnosis was cardio-renal-vascular disease. The patient remained under observation for four years. He died a cardiac death, December 11, 1919. No postmortem could be obtained. Electrocardiographic curves on admission showed subbifurcation block. The accompanying figures show that a change in contour of curves occurred during the first sixteen months, with but little change during the subsequent twenty-one months.

In regard to nearly all of the patients in this group there was sufficient clinical evidence to enable one to make a diagnosis of an underlying cardiosclerosis. That there are exceptions to this rule is shown by the following case:

H. J. M., male, aged fifty-seven years, clerk. Referred by an oculist for relief from headache: no sclerosis of retinal vessels; palpable vessels unusually soft for age; no symptoms referable to heart, which was apparently normal. Blood-pressure, 110–76. The arteriogram showed slight irregularity of the height of the pulse-waves but was otherwise normal; phthalein excretion (intravenous), 78 per cent. in one and a half hours; peridental infection; chronic sinusitis; pulmonary tuberculosis. Of two electrocardiograms taken at an interval of three weeks, both showed subbifurcation block.

The patient was markedly toxic during the period of observation. Unfortunately an opportunity has not arisen to examine him at a time when his heart muscle was carrying a lighter load. It is not impossible that this patient might subsequently have a return to normal contour of electrocardiogram.

Of our 19 patients, 9, or 40.7 per cent., are dead. Of these 6 lived less than four months after block was demonstrated. One died after a period of four years. Two are alive in whom the distortion was noted forty-five and forty-eight months ago.

We believe that the above statistics are confirmatory of the growing belief that a definite deformity of the *Q–R–S* deflections is often associated with extensive myocardial degeneration and that this finding should be sought for as part of routine in the case of patients showing evidence of cardio-renal-vascular disease. Prognosis regarding this group of patients can usually be made by an experienced clinician without laboratory help. However, the routine

examination as carried on in a heart station may be of great value by indicating that certain patients should be referred to an internist before subjecting them to operation or discharging them from the hospital. In occasional cases electrocardiographic evidence of myocardial degeneration may occur in the absence of obvious signs of the disorder. It should be remembered that subbifurcation block may occur as a result of a temporary condition, such as overfatigue or toxemia. Consequently, in doubtful cases repeated observations may be essential.

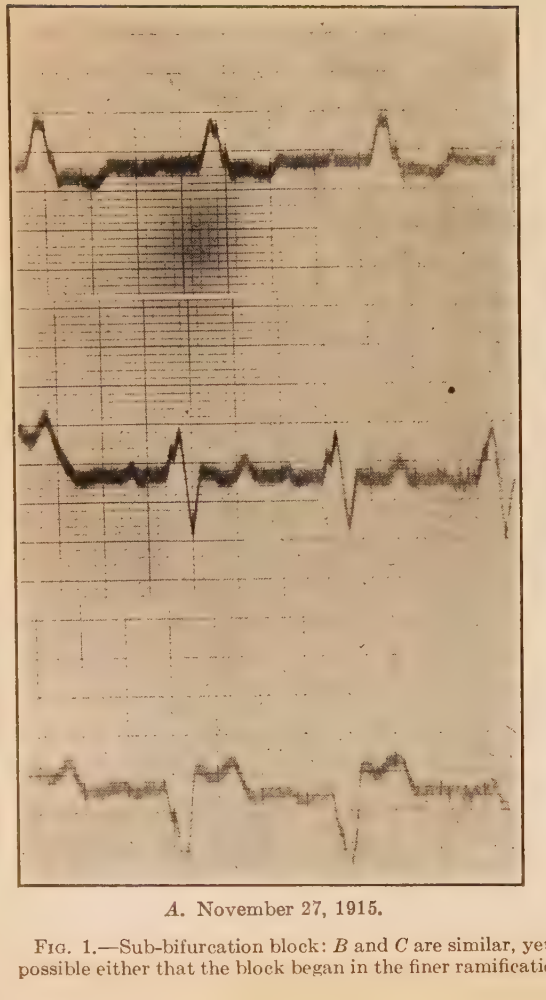
II. Decreased amplitude of primary ventricular deflections may exist in the absence of other distortion of the form of electrocardiogram. There may be considerable variation in the height of the primary complexes in electrocardiograms of normal individuals. Thus, Lewis[5] found that if a series of curves be taken from a number of active students the minimum in the three leads was 1.5, 4 and 2 respectively, while the maximum was 10, 16.5 and 14 scale divisions. The average of 59 students examined was: Lead I, 5.16; Lead II, 10.32; Lead III, 6.61. Nevertheless, Lewis believes that considerable divergence from what is regarded as normal probably indicates that the heart is abnormal. White[6] states that "not infrequently one finds electrocardiographic evidence of a very weak myocardium in cases with a regular pulse. This is shown by one of two findings, a very low flat *T* wave (when one can rule out digitalis) and a small excursion of all waves in all leads." He concludes that very small deflections in all leads usually indicate a very weak myocardium. Frazer[7] noted, as a result of experimentally induced dilatation of rabbits' hearts, that a diminution of the size of all the waves of *Q-R-S* group was observed in degenerative conditions of the heart muscle. Oppenheimer and Rothschild[1] employed low amplitude of the primary ventricular complex as one of the criteria for recognizing the electrocardiogram which was associated with myocardial involvement with a bad prognosis.

In selecting a standard for sorting of our electrocardiograms, we

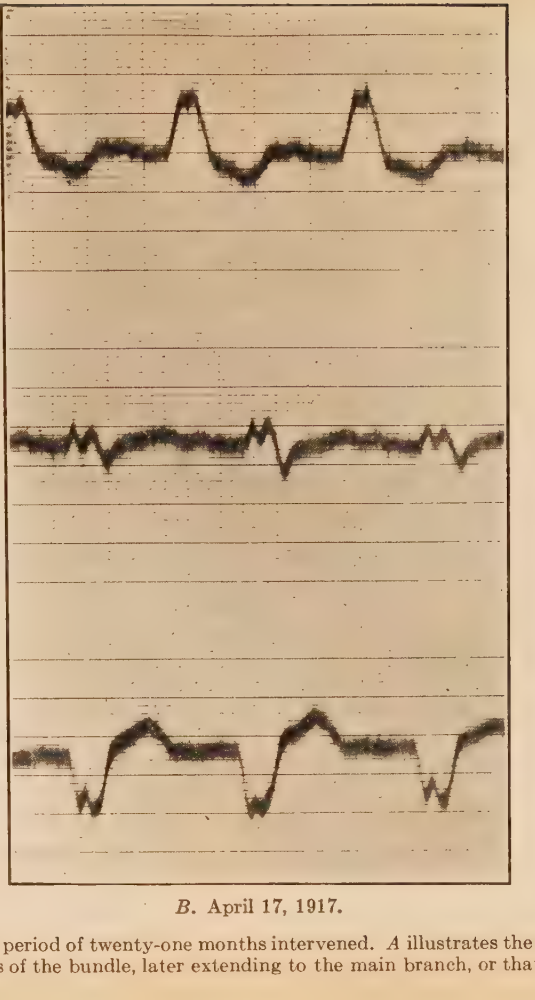
[5] Clinical Electrocardiography, London, Shaw, 1913, p. 22–23.

[6] Diagnostic Value of Electrocardiography of Hearts Beating Regularly, Med. Clinics of North America, January, 1920, iii, 1035.

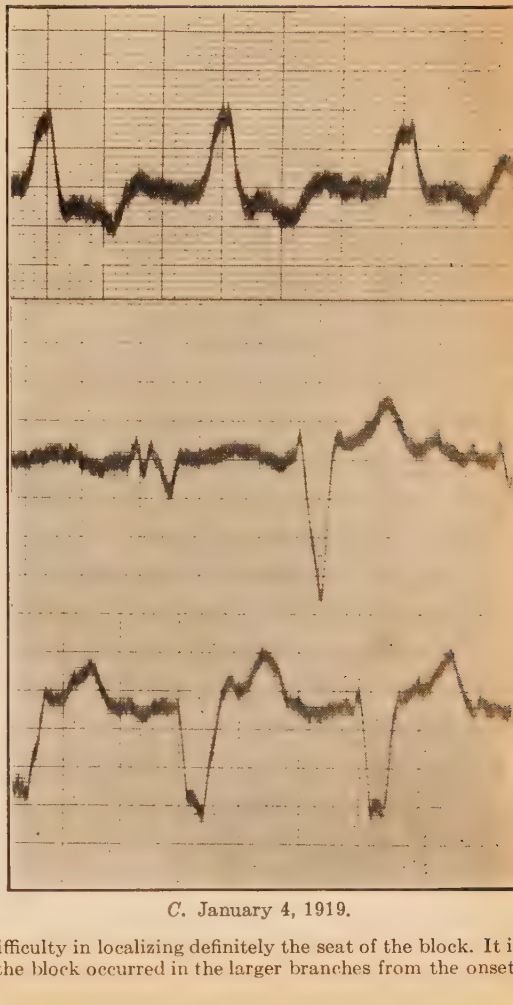
[7] Changes in the Electrocardiograms Accompanying Experimental Changes in Rabbits' Hearts, Jour. Exper. Med., September, 1915, xxii, 292.



A. November 27, 1915.



B. April 17, 1917.



C. January 4, 1919.

FIG. 1.—Sub-bifurcation block: *B* and *C* are similar, yet a period of twenty-one months intervened. *A* illustrates the difficulty in localizing definitely the seat of the block. It i possible either that the block began in the finer ramifications of the bundle, later extending to the main branch, or that the block occurred in the larger branches from the onset

have accepted ten scale divisions as the average normal. This has been done in full realization that each patient must establish his own normal and that any standard is therefore an artificial one. At most such deductions can be only inferential. Further sources of

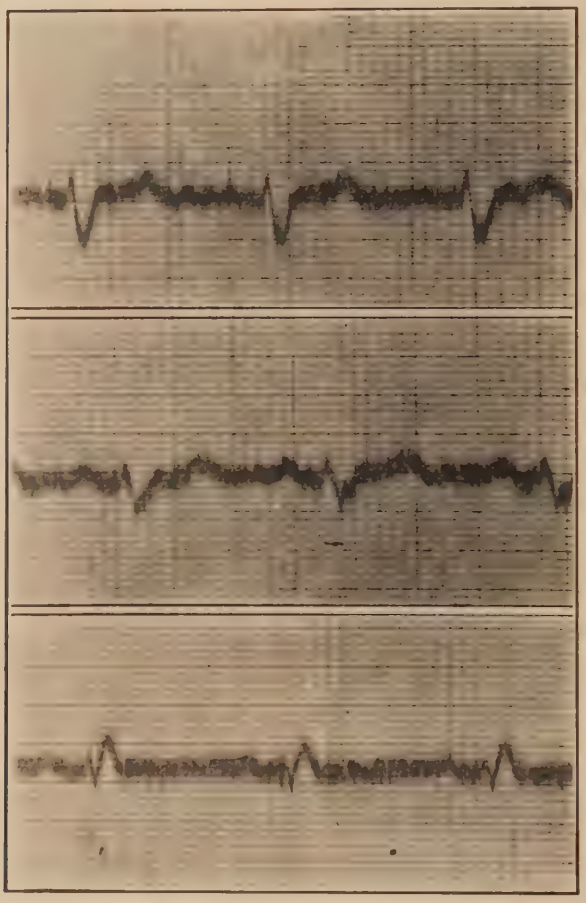
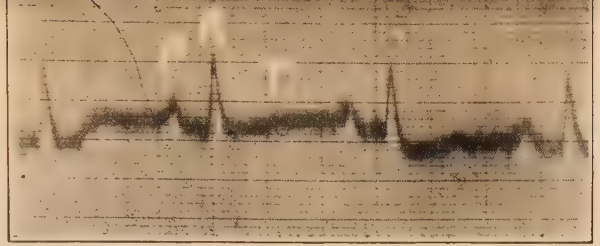
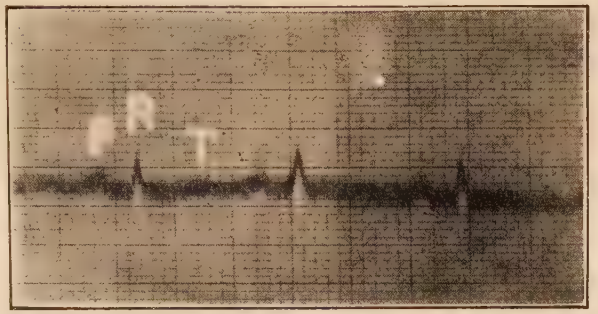


FIG. 2.—Sub-bifurcation block: Occurring in a patient without symptoms, suggesting cardiac disease. H. J. M., aged fifty-seven years. Referred by an oculist because of headaches.

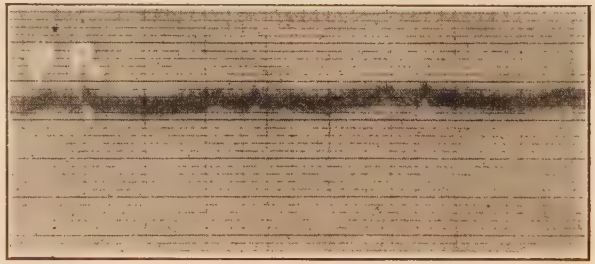
error may be due to instrumental defects and faulty technic. There was an occasional unexplained variant as illustrated in Fig. 4. In numerous instances the possibility of instrumental defect appears to have been excluded definitely by the fact that control electro-



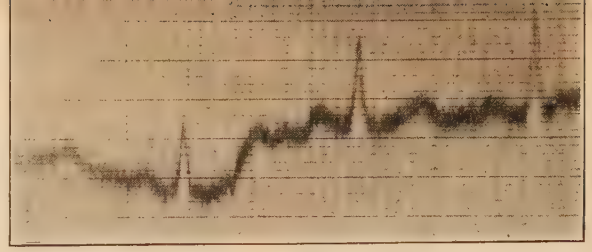
A. February 3, 1920. E. F. D., aged twenty-four years. Serofibrinous pericarditis of tuberculous origin; effusion, later becoming purulent. Patient able to walk without dyspnea.



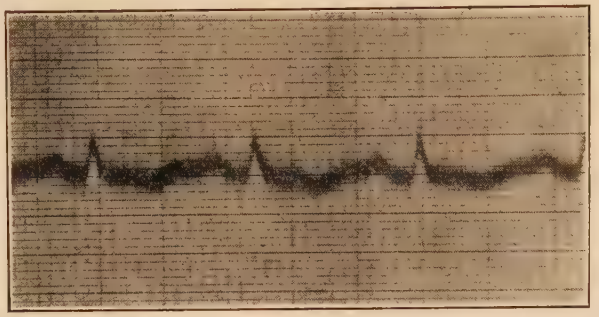
B. March 29, 1920. Effusion more marked. Decompensation severe.



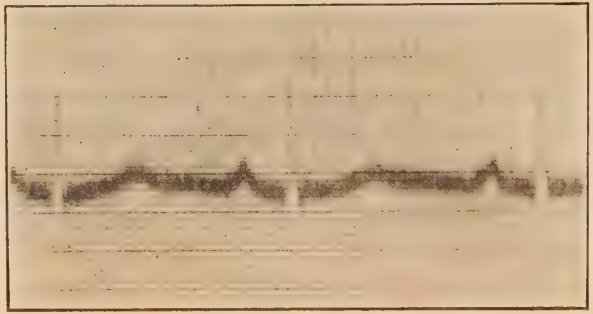
C. April 16, 1920. Forty hours after drainage of pus from pericardial cavity. Extreme weakness. Circulation poorly maintained.



D. April 16, 1920. Control.

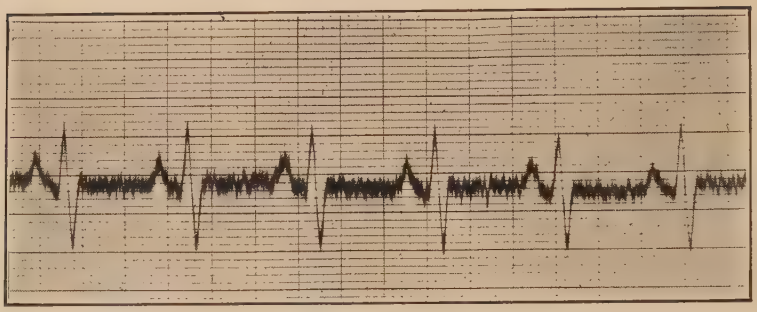


E. April 29, 1920. Increased amplitude thirteen days after operation. Subjective and objective improvement.

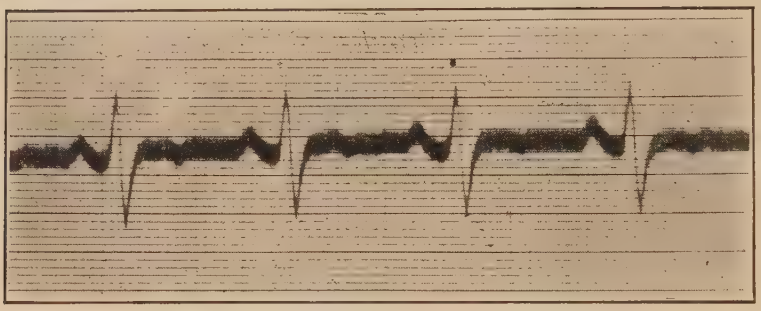


F. April 29, 1920. Control.

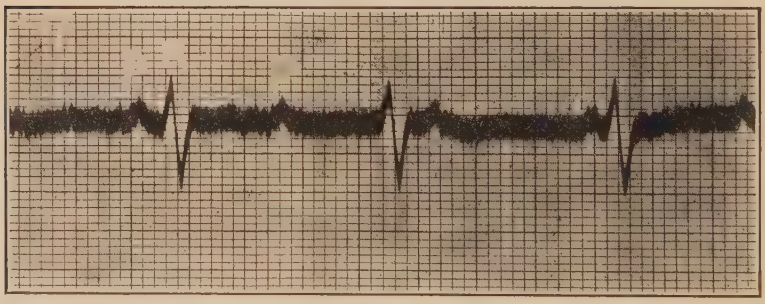
FIG. 3.—Decreased amplitude. Height varying with clinical condition.



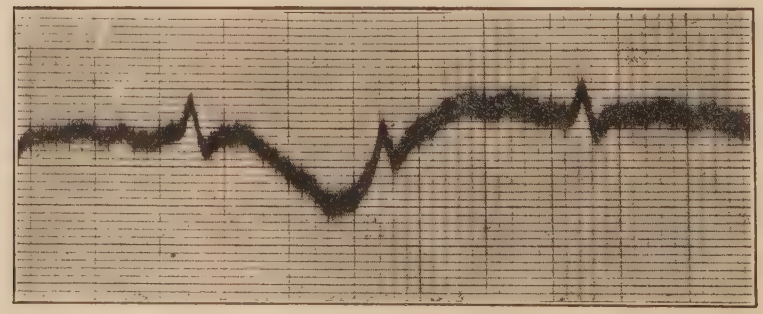
A. June 13, 1916.



B. February 3, 1917.

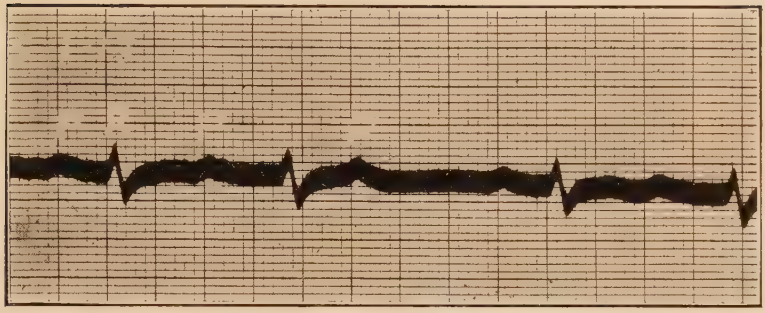


C. March 6, 1917.

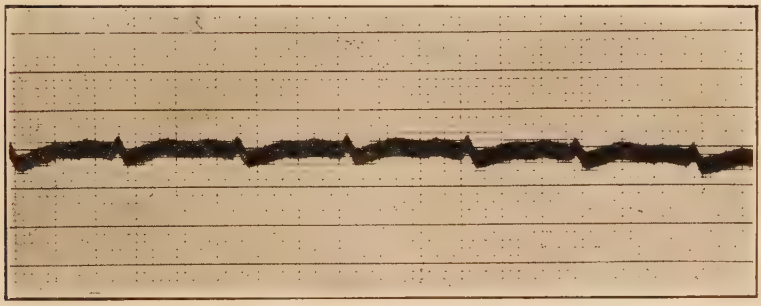


D. April 6, 1917.

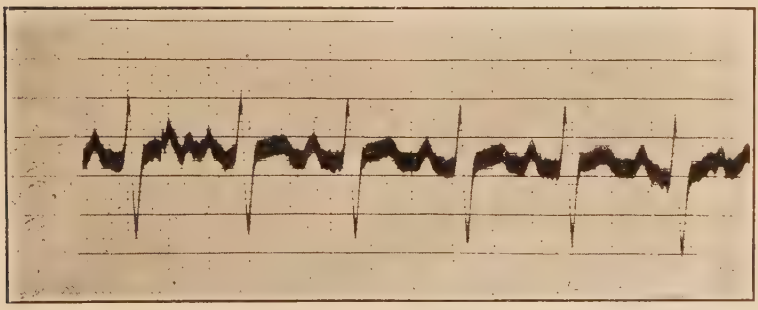
FIG. 4.



E. May 1, 1917.



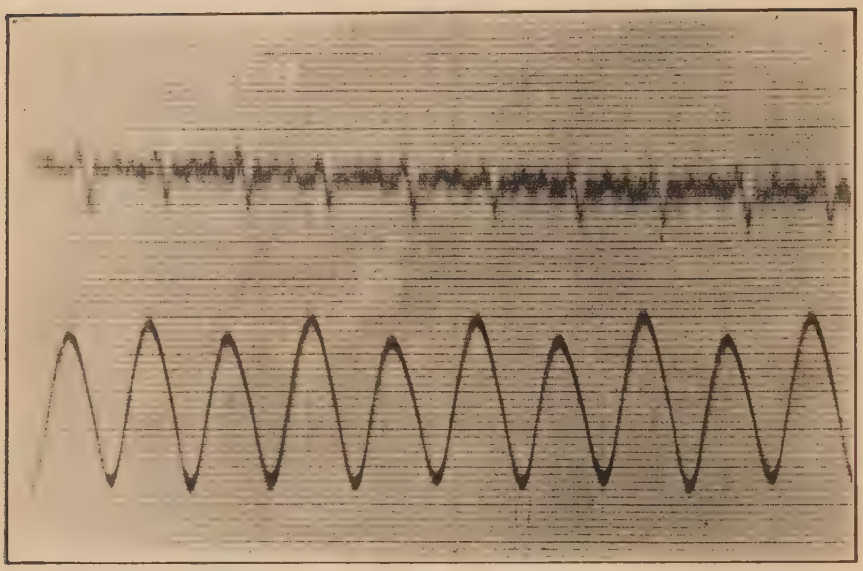
F. May 15, 1917.



G. May 18, 1917.

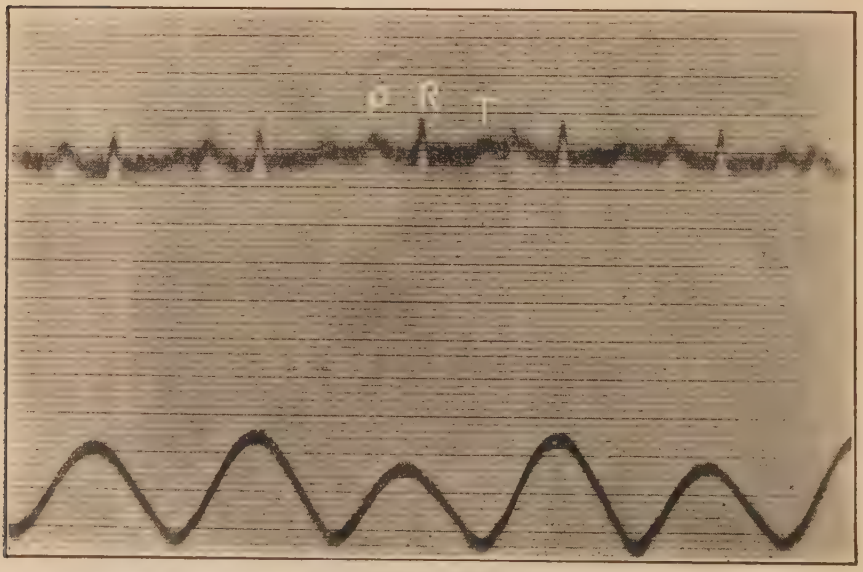
FIG. 4*a*.—Decreased amplitude. Height varying with clinical condition during period of eleven months; sudden return to normal amplitude nineteen days before patient's death and at period when decompensation was profound. R. G., aged seventy-eight years. Acute endocarditis, superimposed upon chronic mitral and aortic valvular disease. Chronic myocarditis; pulsus alternans.

cardiograms gave normal deflections. In a small group of patients there existed so striking a parallelism between lower amplitude and



A. Pulsus alternans.

FIG. 5.

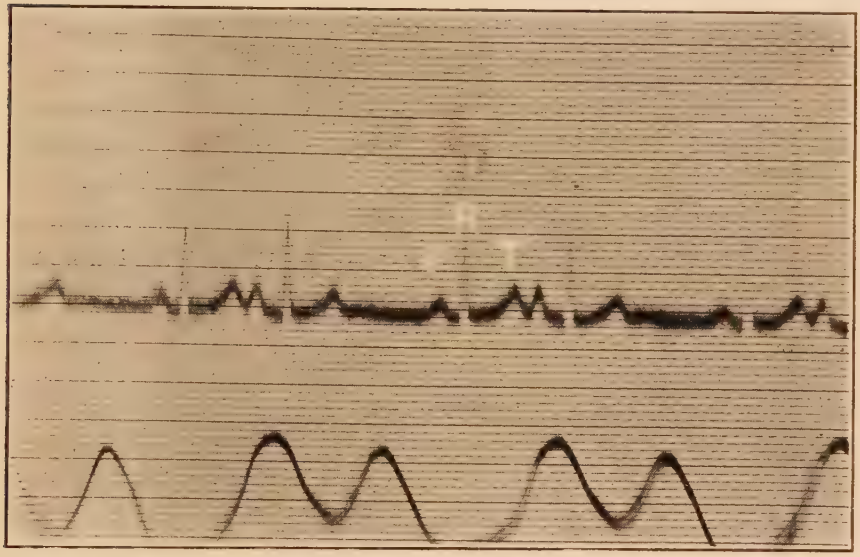


B. Pulsus alternans.

FIG. 5*a*.

increasing myocardial insufficiency that the association could hardly have been accidental in all of them.

Of our patients, 46, or 5.8 per cent., showed constant or occasional low voltage in all leads; 56 per cent. were females. The age incidence differed widely. The mortality was relatively high: 17, or 36 per cent., are dead. Of the total deaths, 76 per cent. occurred in patients in the fifth decade.



C. Coupling due to premature beats; patient referred to heart station as case of supposed alternation.

FIG. 6.—Type of tracing obtained by apparatus illustrated in Fig. 7.

The following case illustrates a changing amplitude exactly parallel to the clinical condition at the time the records were taken. It is believed that the electrocardiograms may be depended upon as each record was checked by control patients.

E. F. D., male, aged twenty-four years, admitted February 3, 1920. Clinical diagnosis; pericardial effusion; at first serous; later purulent. Effusion drained, April 14, 1920. The primary deflection of first electrocardiogram was eight scale divisions. This record was taken at a time when the patient was able to walk about, with apparent comfort. Subsequent curves taken at periods during which the patient's clinical condition became progressively worse,

showed a progressive diminution in amplitude to two scale divisions. A final record taken during a period of improvement after operation showed a return to wider deflections (four scale divisions).

That conclusions based on progressive decrease of amplitude might result in error is exemplified by the following:

R. G., female, aged seventy-eight years. Admitted May 11, 1916. Clinical diagnosis: acute endocarditis superimposed upon chronic mitral and aortic valvular disease; chronic myocarditis; pulsus alternans. Clinical condition of patient became progressively worse while in the hospital. Electrocardiogram on admission showed normal height of deflections, ten scale divisions, Lead I. Patient discharged November 2, 1916, no further electrocardiogram being taken. Readmitted January 4, 1917. Patient died June 6, 1917. Patient's clinical condition became progressively worse after second admission. The amplitude of the primary deflections became gradually smaller (from seven to one scale divisions). However, there was one striking exception; a final electrocardiogram nineteen days before death showed that the deflections had returned to ten scale divisions.

III. Prolongation of the *P–R* interval over the normal of 0.2 second may be due to various causes such as acute infections, drug action and degenerative processes affecting heart muscle. There is considerable difference of opinion among observers as to the normal *P–R* interval. Lewis[8] states that "prolongation over 0.20 second is never found in healthy hearts." Hecht[9] regards 0.14 as normal; F. N. Wilson[10] accepts 0.17. Within certain limits each patient sets his own standard. Cohn, Jamieson and Frazer[11] have shown that digitalis can prolong the *P–R* interval. Hence unless digitalis influence can be excluded, no conclusions as to prognosis can be based upon prolongation of the *P–R* interval. Such deductions could not be made in patients of our series since regarding most of them no reliable history as to previous medication was available.

[8] Vide supra, p. 37.

[9] Der Mechanismus der Herzaktion im Kindersalter, seine Physiologie und Pathologie, Ergeb. d. inn. Med. u. Kinderh., Berlin, 1913, ii, 324; quoted by Rupe: Mod. Med., March, 1920, ii, 215.

[10] Recent Progress in Pediatrics, Résumé on the Circulation, Am. Jour. Dis. Children, 1915, x, 376, quoted by Rupe, Loc. cit., p. 215.

[11] The Influence of Digitalis on the T-wave of the Human Electrocardiogram, Jour. Exper. Med., June, 1915, xxi, 593.

On the other hand it is exactly in the type of patient in which a prolongation of P–R interval might be expected that digitalis is most liable to be administered.

IV. Since such inversion is always or nearly always pathologic, according to Lewis[12] inversion of T_1 "is often associated with signs or symptoms of ill omen." This author published figures[13] in which an invert T_1, which followed temporary deformity of primary ventricular complex, became upright when that deformity disappeared. The first curve was taken during a febrile attack, the second, one day later, after the subsidence of fever. Willius[4] states that a close connection exists between inversion of T_1 and disease of myocardium. Cohn[11] and his associates have shown that digitalis can modify T in that a T which was upright in the initial curve may be lowered first and finally inverted. Inversion of T_1 has been noted by White[6] in connection with hypothyroidism, the T "tending to become more positive" in the presence of clinical improvement during thyroid feeding. Morrison[14] has noted that changes in the electrocardiogram following bleeding, hot-packs, ingestion of water and fasting may in certain persons affect the form of the electrocardiogram. Harris[15] while admitting that digitalis may affect T_1, draws definite conclusions on inversion of T_1 as observed in 16 of 40 patients electrocardiographed in an out-patient clinic. The cases electrocardiographed were selected on account of dyspnea on exertion, fainting fits and edema. Apparently no history of previous medication was sought, since no mention of absence of digitalization is made in this author's text or accompanying table; yet Harris has the temerity to conclude that "an invert T in the Lead I is reliable evidence of a damaged heart muscle."

Fifty-three cases in our series show inversion of T_1. In 26 of these T_1 was inverted alone. In only 1 case was it possible definitely to rule out digitalis. Hence we are unable to draw any deductions as to the significance of invert T_1 as personally observed.

[12] Clinical Electrocardiography, London, Shaw, 1913, p. 28.
[13] Idem, p. 29.
[14] Changes in the Electrocardiogram due Possibly to Alterations in Blood Volume, Proc. Soc. Exper. Biol., and Med., 1916–1917, xix, 64.
[15] Significance of an Inverted "T" in the First Lead of the Cardiogram, Lancet, February, 1919, i, 168.

V. From the standpoint of prognosis, alternation of the pulse, as occurring in hearts beating at an approximately normal rate, is a finding of extreme gravity. Unfortunately the electrocardiograph is capable of recording only the alternation of heart-action currents. The fact that curves showing such a disturbance of mechanism are rare is confirmed by our series in which the finding was present regarding but 0.55 per cent. of all patients examined. It is unfor-

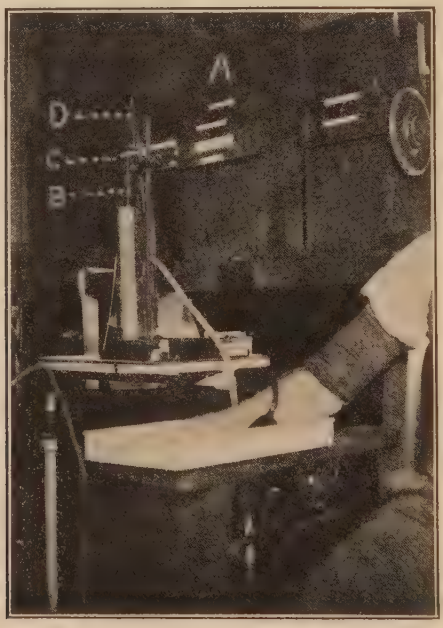


FIG. 7.—Recording apparatus for reading pulse waves in connection with simultaneous electrocardiogram; used for detection of pulsus alternans. *A*, camera; *B*, straw attached to cork float which rides on mercury; *C*, transverse arm of lever, which rests on straw; *D*, upright arm of right-angled lever, which oscillates in front of camera lens.

tunate that the electrocardiograph is incapable of demonstrating he disturbance of mechanism underlying the alternating pulse, since the latter finding, if sought for as routine, is found to be of frequent occurrence. Obviously, the value of the string galvanometer would be enhanced if it were possible to record simultaneously electrocardiograms and pulse-waves. Our discussion of alternation will be limited to the description of an apparatus which we have devised to fulfil this indication.

The device which we are using combines the simplicity of the

cuff method of Herrick[16] with the accuracy of the electrocardiogram. It therefore obviates the various sources of error of the former while preserving much of its simplicity of application. Used by us first only when a sphygmograph was not available, it is now used as routine on all arteriosclerotic patients and on those exhibiting premature contractions. The apparatus which is both time-saving and inexpensive may be visualized by reference to the accompanying illustration (Fig. 7).

The oscillations of the mercury column of a sphygmomanometer are transferred to a right-angled lever, the upright arm of which moves in front of the slit of the camera of an electrocardiograph. The cuff of the sphygmomanometer is applied in the usual manner and the tracing is taken at a pressure slightly below that ordinarily accepted as the systolic pressure.

We claim no originality in the production of a combined electrocardiogram and pulse-tracing. Methods of producing such combined records abound. It is even quite possible that other investigators have employed the principle upon which our appliance is based. As we have seen no reference in the literature to such an application, however, we feel justified in describing it here. The accompanying figures are illustrative of the results obtained.

Conclusions.—1. Electrocardiographic curves are capable of furnishing important information as to the efficiency of the heart muscle.

2. As cardiac failure is due to myocardial insufficiency the electrocardiograph can furnish information valuable from the standpoint of prognosis.

3. Conduction defects below the bifurcation of the bundle of His may be associated with a characteristic electrocardiogram. It is often difficult to determine whether such defect is in the branch bundle or in the terminal arborization. The defect may be functional or it may be due to histologic change. In the latter case the prognosis is grave.

4. Decreased amplitude of the primary ventricular deflections is at times found to have a striking relationship to clinical evidence of a failing heart. Exceptions to this relationship occur, and, as

[16] Pulsus Alternans Detected by the Sphygmomanometer, Jour. Am. Med. Assn., February, 1915, lxiv, 739.

there are several possible sources of error in obtaining reliable curves, observations should be carefully controlled and definite conclusions withheld until the subject is further elucidated.

5. Prolongation of $P–R$ interval and inversion of T_1 have been associated by various observers with degenerative processes in heart muscle. A prolongation of $P–R$ and an inversion of T_1 can also be brought about by digitalis action, and it is precisely in the class of cases in which information as to the $P–R$ interval and inversion of T_1 could be of value that digitalis is liable to have been administered. Conclusions as to the condition of heart muscle as based on the presence of one or the other of these deformities must be confined to patients from whom digitalis effect can be excluded. Analysis of our series has shown that digitalis effect can seldom be excluded in such patients as are routinely referred to a heart station. Hence, prolongation of $P–R$ and inversion of T_1 are liable to be of little prognostic significance in such patients.

6. A discussion of pulsus alternans does not come properly within the scope of this paper, since the underlying disturbance of mechanism can seldom be demonstrated by the string galvanometer. This fact is unfortunate, since the recognition of an alternating pulse carries with it so grave a prognosis that the search for this finding should be routine in certain classes of patients. A simple device is described whereby galvometric curves and pulse waves can be simultaneously recorded. This can be done with but little expenditure of time, and the method has therefore become routine in our laboratory.

7. The practical value of laboratory evidence as to the presence of disease of the heart muscle is inversely proportionate to the skill of the attending physician in interpreting clinical evidence as to the imminence or presence of heart failure. Such skill is possessed chiefly by the internist. Yet internists furnished 61.5 per cent. of all cases examined. The statistics of other heart stations would probably be similar. It becomes, therefore, the duty of the internist to instruct members of other branches of the profession regarding the necessity of more frequent use of instruments of precision in the diagnosis and prognosis of disease of heart muscle.

Note.—The authors acknowledge their indebtedness to Dr. A. P. D'Zmura for assistance in the preparation of this paper.

CHEMICAL STUDIES OF EDEMA

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This paper will give merely a preliminary presentation of results of comparative analyses of blood and various body fluids. The literature of the subject and conclusions on the several problems involved will be deferred to a more complete later publication.

All figures in the tables represent milligrams per 100 c.c., with the exception of the CO_2 capacity, which is expressed in the usual form of volume per cent. The creatinine analyses were performed by Dr. Cyrus Field, to whom thanks are due for this aid. The term "blood" is used for the sake of brevity in tabulation, but unless otherwise specified, it is to be understood that analyses for urea and creatinine were performed upon the whole blood, and those for sugar, chlorides and bicarbonate (CO_2 capacity) upon the oxalated plasma. The methods used were as follows: For sugar, Benedict; for chlorides, McLean-Van Slyke-Donleavy; for CO_2 capacity, Van Slyke; and the urease method for urea.

I. Miscellaneous Analyses

Table I illustrates the unequal distribution of the different substances in the different body fluids in a mixed series of cases of diabetes, nephritis, vascular hypertension and arteriosclerosis. No specific differences of distribution were found in the different diseases.

TABLE I.—PARALLEL ANALYSES OF BODY FLUIDS.

Exam.	Fluid.	Urea.	NaCl.	Sugar.	CO^2.	Creatinine.	Nitroprusside reaction.	Diagnosis.
1	Blood	27.1	574	117	65.3	1.4	...	Chronic nephritis; mitral regurgitation.
	Ascitic	20.8	571	187	71.0	1.1	...	
	Spinal	41.6	661	108	51.9	1.0		
2	Blood	36.4	586	124	40.4	1.7	...	Chronic nephritis; mitral regurgitation.
	Ascitic	25.5	616	137	61.4	1.4		
	Spinal	..	668	80	54.8	1.0		
3	Blood	15	559	142	82.5	..	...	Arteriosclerosis and arterial hypertension.
	Spinal	8	675	115	77.7			
4	Edema	32	570	109	80.5	..	...	Diabetes.
	Blood	..	..	162				
5	Blood	20	520	439	51.0	..	Slight +	Diabetes.
	Edema	24	590	516	56.5	..	Heavy	
6	Blood	18	543	381	51.9	..	Slight	Diabetes.
	Edema	14	583	237	62.3	..	Mod. +	
7	Blood	266	595	162	30.9	5.0	0	Chronic interstitial nephritis and diabetes.
	Pleural	242	615	179	23.3	5.0	0	
8	Blood	196	540	263	25.2	4.2	...	Chronic interstitial nephritis and diabetes.
	Ascitic	188	545	414	15.7	5.0		
9	Blood	22	535	381	55.7	..	Mod.	Diabetes.
	Edema	16	550	402	66.2	..	Mod. +	
10	Blood	18	540	376	65.3	..	Slight	Diabetes.
	Edema	10	573	381	69.1	..	Slight +	
11	Blood	24	550	263	78.7	..	Faint +	Diabetes.
	Edema	25	535	241	78.7	..	Faint +	
12	Blood	22	510	268	79.6	..	0	Diabetes.
	Edema	18	535	273	82.5	..	Faint +	
13	Blood	21	525	273	62.3	..	Faint +	Diabetes.
	Edema	30	550	273	76.7	..	Mod.	
14	Blood	24	500	362	78.6	..	Faint	Diabetes.
	Edema	20	485	352	93.0	..	Heavy	
15	Blood	207	566	256	49.2	..	...	Chronic interstitial nephritis and diabetes.
	Edema	219	582	243	48.4	..	...	
16	Blood	218	558	..	43.4	..	...	Chronic interstitial nephritis.
	Edema	181	614	..	51.9			
17	Blood	..	570	177	69.1	..	...	Chronic nephritis; diabetes.
	Edema	..	595	202	61.4	..	...	
18	Blood	206	566	222	54.8	1.2	...	Chronic interstitial nephritis and diabetes.
	Edema	229	614	176	64.3	0.4		
19	Blood	28	533	..	..	..	....	Arterial hypertension.
	Blister	16	476					
20	Blood	20	539	180	69.1	1.5	...	Diabetes.
	Edema	20	589	150	84.3	0.8		
21	Blood	242	559	138	61.6	..	...	Diabetes.
	Edema	239	617	146	60.6	..	...	
22	Blood	28	597	170	70.0	1.1	...	Diabetes.
	Edema	26	559	161	..	0.4		
23	Blood	25	547	163	70.0	..	....	Diabetes.
	Ascitic	34	586	212	69.1			
24	Blood	25	559	143	59.5	3.0	...	Chronic interstitial nephritis and diabetes.
	Ascitic	19	597	180	62.4	1.0		
25	Blood	17	563	306	..	1.0	...	Arterial hypertension.
	Spinal	17	676	86	..	2.3		
26	Blood	27	548	107	33.8	3.6	...	Chronic interstitial nephritis.
	Ascitic	36	567	142	52.0	1.5		
	Spinal	23	648	101	37.6	1.4		
27	Blood	20	550	241	76.7	..	...	Diabetes.
	Edema	20	530	241	76.7			
28	Blood	18	543	381	51.9	..	0	Diabetes.
	Edema	14	583	237	62.3	..	0	
29	Blood	10	532	111	61.4	..	0	Chronic parenchymatous nephritis.
	Edema	12.5	582	143	89.1	..	0	
30	Blood	10	532	109	52.8	..	0	Chronic parenchymatous nephritis.
	Edema	10	582	155	83.2	..	0	
31	Blood	14	515	100	52.0	1.0	0	Chronic parenchymatous nephritis.
	Edema	10	597	160	79.2	0.4	...	
32	Blood	8	571	100	86.2	2.0	...	Chronic parenchymatous nephritis.
	Edema	12	590	147	78.6	0.2		
33	Blood	10	520	166	59.1	1.0	...	Chronic parenchymatous nephrtis.
	Edema	12	590	150	82.5	0.2		
34	Blood	12	582	106	81.5	1.5	...	Chronic parenchymatous nephritis.
	Edema	12	605	142	68.1	0.2		
35	Blood	14	590	108	69.1	1.5	...	Chronic parenchymatous nephritis.
	Edema	18	605	147	79.5	0.3		
36	Blood	10	528	138	72.0	1.2	...	Chronic parenchymatous nephritis.
	Edema	8	582	156	81.5	0.5		

Spinal fluid is illustrated by Cases 1, 2, 3, 25, 26. The only rule without exceptions is that the chloride concentration is far higher than in any other body fluid, in accord with numerous analyses in the literature. No fixed ratio, however, can be determined between the two. In the majority of instances the other substances under examination have a lower concentration in the spinal fluid than in the blood, but exceptions occur and the ratios are very variable.

The fluid of a blister produced by cantharidal plaster was examined in Case 19 and found lower than the blood in urea and chloride.

The series also affords 5 examples of ascitic fluid, one (No. 7) of pleural fluid and 26 of limb edema. No law of distribution can be deduced except that the ratio of concentration between the blood and the extravascular fluid is highly variable. The closest similarity and the most numerous instances of identical values are found in the urea, but the observations do not support a commonly held conception of a strictly uniform distribution of urea throughout the tissues and fluids of the body. In a majority of cases the substances with the strongest osmotic power, namely, the chlorides and the bicarbonates, are in higher concentration in the fluid outside the vessels than inside the vessels, so that the fluid might appear to be held in the tissue spaces by the osmotic influence of the retained salts. Opposite examples occur, however, in which the fluid appears to be retained in spite of an osmotic influence in the opposite direction.

II. Administration of Test Substances

The following experiments are of a different character from any heretofore reported in the literature, and consist in oral administration of various substances followed by parallel analyses of blood and edema fluid at short intervals. They were performed upon a Greek patient, aged nineteen years, with so-called "nephrosis," characterized clinically by very heavy albuminuria, marked edema which resisted months of strictest salt-free diet, and moderate weakness and anemia, along with a practical absence of other clinical symptoms, normal blood analyses and fairly good kidney functions in tests on the Ambard principle, though the suspicion existed of a specific impairment of water excretion.

Experiment I. Glucose Test. (Chart I.)

The patient drank a solution of 100 gm. glucose in 200 c.c. water, fasting at breakfast time. Thereafter 200 c.c. water was given hourly by mouth and blood and edema fluid collected. A rise of the plasma sugar to 172 mgm. per 100 c.c. occurred at the end of

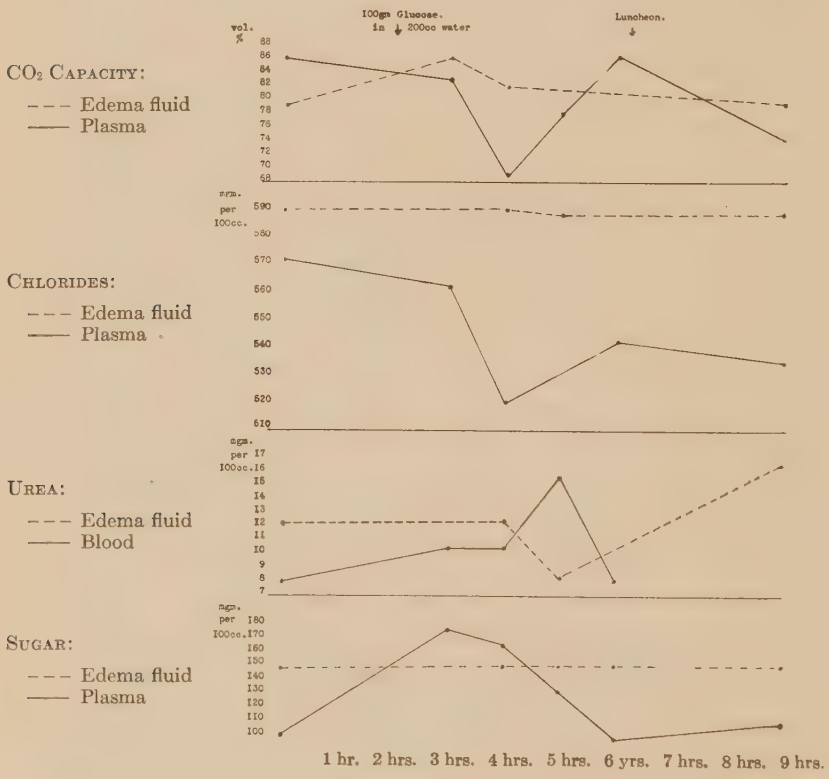

CHART I

three hours. The fasting values in this patient were normal, but a lowered glucose tolerance is suggested by this hyperglycemia from glucose and the slow return to normal in six hours. Glucose in the edema fluid remained constant at 145 mgm. per 100 c.c. The reason for this relatively high constant figure is unknown. The chloride and bicarbonate concentration of the plasma fluctuated

inversely to the curve of hyperglycemia. In the edema fluid the concentration of bicarbonate changed only slightly and that of chlorides not at all. The blood urea rose like the sugar, though the peak of the curve came later. The urea concentration in the edema fluid fell as that in the blood rose, then rose markedly as that in the blood fell.

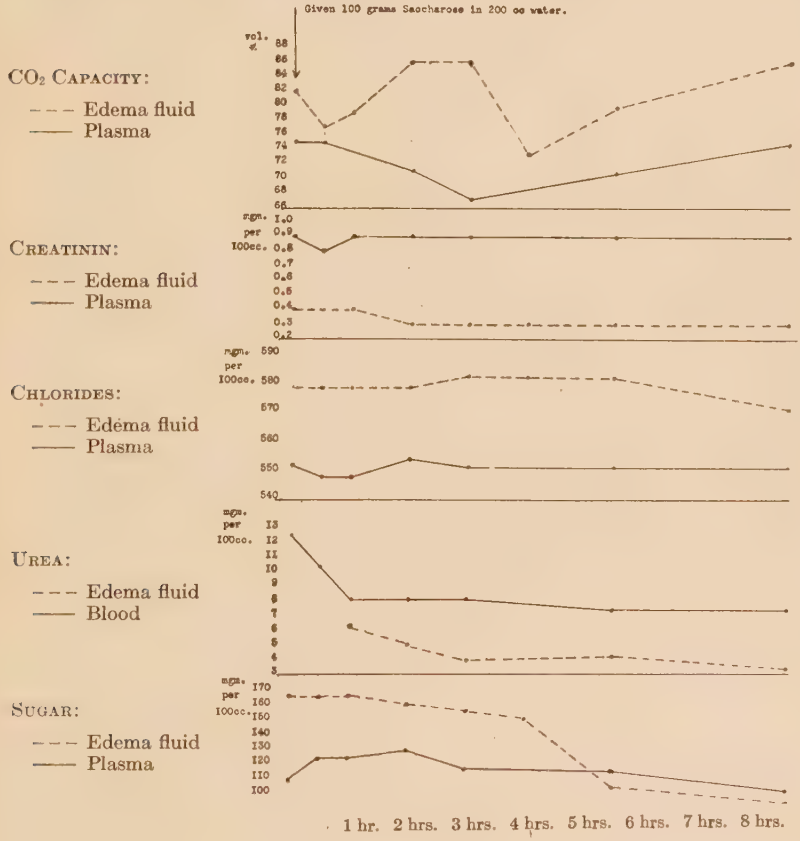

CHART II

Experiment II. Saccharose Test. (Chart II.)

The program was as before, except that 100 gm. saccharose was given instead of glucose. The plasma sugar rose from 109 to 123 mgm. per 100 c.c. at the end of two hours, then fell with fasting to

101 mgm. The sugar in the edema fluid began at the remarkably high level of 166 mgm. per 100 c.c., and instead of rising fell, especially between the fourth and fifth hours, so that at the end it was slightly below the plasma sugar concentration. The urea concentration in blood and edema fell at first, then held practically stationary. The creatinine and also the chlorides were practically unaffected. The bicarbonate showed fluctuations in the plasma and still more in the edema fluid, without any clear explanation.

Experiment III. Protein Test. (Chart III.)

A test with ingestion of 50 gm. protein was performed as described by Jacobsen.[1] The protein was taken in the form of lean beefsteak, together with 200 c.c. water; 200 c.c. water was also taken every two hours thereafter. As was to be expected the chief effect was upon the blood urea, which rose steeply to the fourth hour, then fell almost as sharply. The urea content of the edema fluid was barely affected, the result being that though the concentrations in blood and edema were close together at the beginning and end there was a marked divergence in the middle of the digestive curve. The creatinine was unaffected. The plasma sugar began at 100 mgm. per 100 c.c., was scarcely altered in four hours, but rose to 131 mgm. at the sixth hour. The edema sugar, as usual in this patient, began at a higher level, namely, 128 mgm. per 100 c.c. It rose markedly in four hours to 190 mgm., then fell to the usual fasting level. Though no salt was taken with the meat the plasma chlorides rose markedly between the second and fourth hours. The chlorides of the edema fluid remained unaltered. The CO_2 capacity of the plasma rose, with fluctuations, while that of the edema fluid rose a trifle. To form some idea of the blood volume or concentration the corpuscle volume was recorded after thorough centrifugation and indicated dilution of the blood.

Still greater dilution of the blood was obtainable in this patient in other tests with ingestion of nothing but large quantities of water, while the body weight correspondingly rose. The urine secretion in Experiments 1, 2 and 3 was so small that the patient was unable to void at the close of any of them. It must therefore be recognized

that the concentration of most substances in the plasma rose during this dilution of the blood while the concentration in the edema fluid did not, as a rule, suffer any corresponding fall.

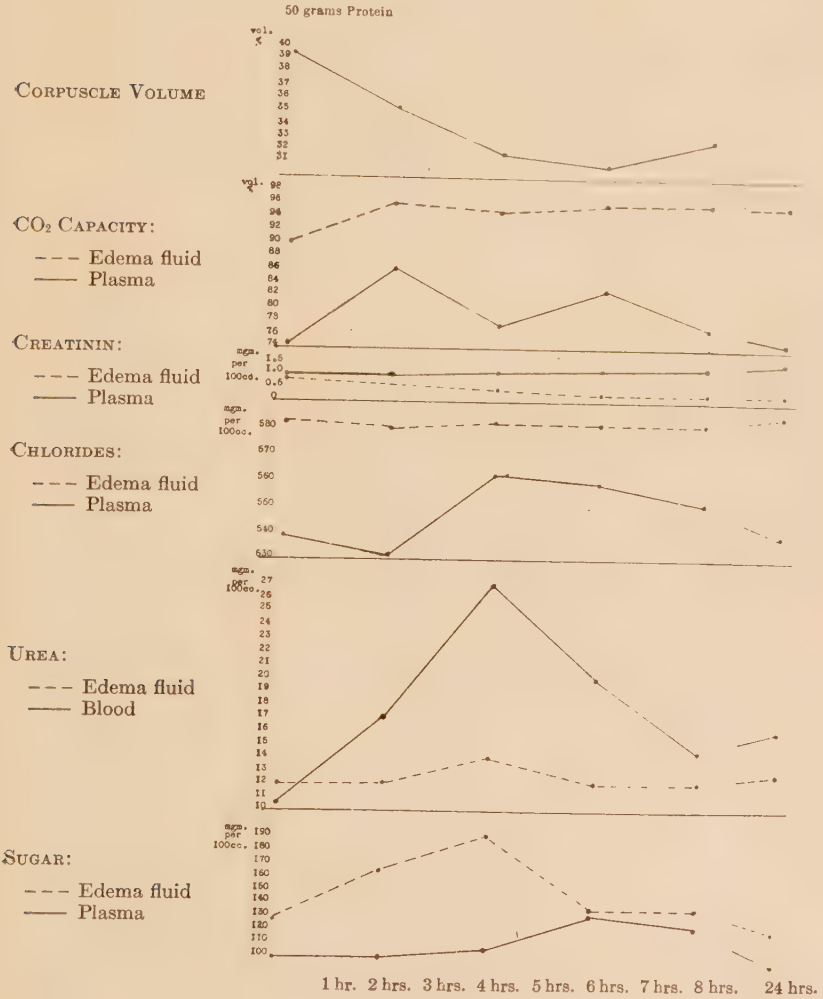

CHART III

Experiment IV. Salt Test. (Chart IV.)

A dose of 10 gm. pure sodium chloride in 100 c.c. water was taken by mouth in the fasting condition. Nothing was taken thereafter,

the regular water ingestion mentioned in the other experiments being omitted. In addition to the blood and edema fluid shown in

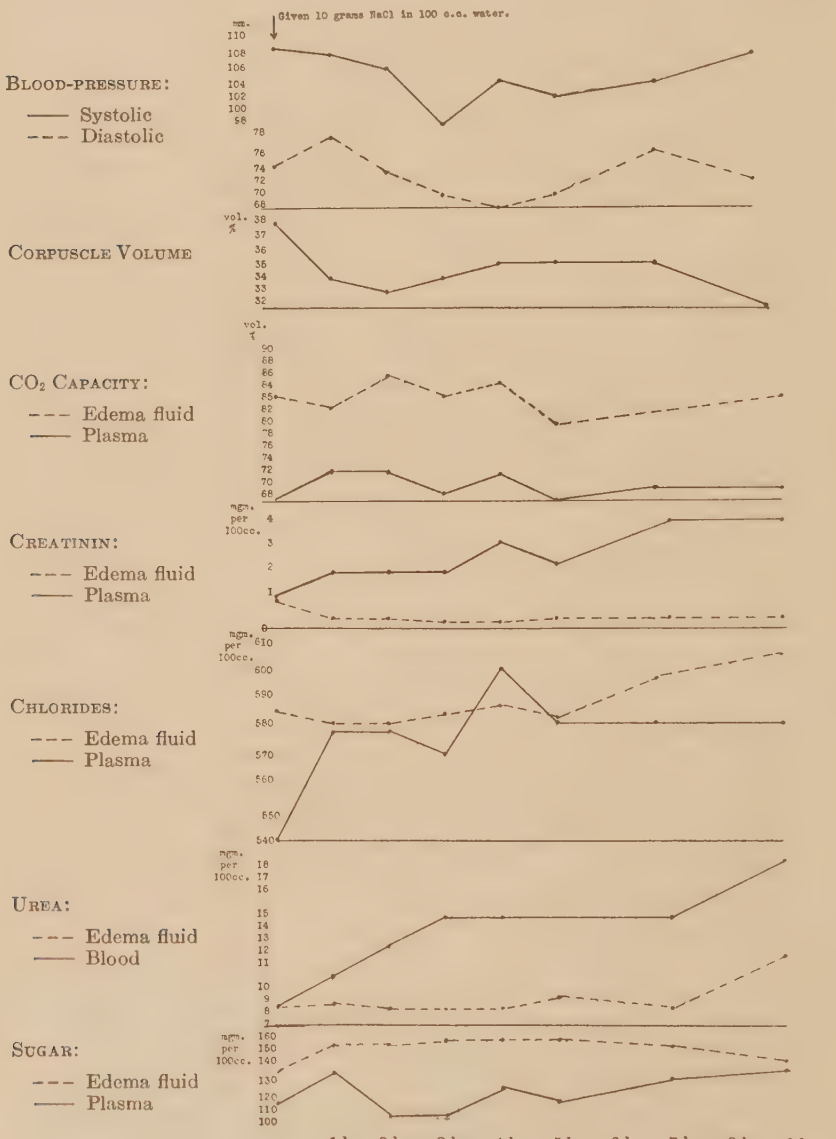

CHART IV

Chart IV, urine specimens were obtained as shown in Table II. The diet had been strictly salt-free for three months before this test.

TABLE II

Hour.	Blood-pressure. Systolic.	Diastolic.	Urine, volume.	Total chlorides, grams.	Urea, mg. per 100 c.c.
1	109	74			
	108	78	11	0.02	311
2	106	73	10	0.02	360
3	98	70	10	0.02	396
4	104	68	12	0.02	360
5	102	70	9	0.02	396
6	...	..	0		
7	104	76	15	0.02	522
8	104	76	0		
9	108	72	19	0.02	510

The plasma chlorides, beginning at 540 mgm. per 100 c.c., rose very sharply and reached a maximum of 602 mgm. at the fourth hour. The chloride concentration of the edema fluid began at a much higher level, namely, 586 mgm. per 100 c.c., and held practically stationary for five hours. From the fifth to the eighth hour, while the plasma chloride concentration was holding stationary at 582 mgm. that in the edema fluid rose to 606 mgm.

The bicarbonate concentration meantime remained essentially unchanged.

The plasma sugar underwent irregular fluctuations while that in the edema fluid maintained almost a steady plateau.

The blood urea rose markedly from an initial 8.3 mgm. to 18.7 mgm. per 100 c.c. at the close of the experiment. The urea concentration of the edema fluid remained practically unchanged for seven hours, then between the seventh and the ninth hour rose from 8.2 to 12.5 mgm. per 100 c.c.

The creatinine in the blood rose somewhat like the blood urea while the concentration in the edema fluid fell slightly and then remained stationary.

The corpuscle volume indicated a slight dilution of the blood. The supposition that water was selectively withdrawn from the edema fluid might help to explain the final rise of chlorides, urea and creatinine in the edema fluid; but there is no regular parallelism in the curves and the concentrations of sugar and bicarbonate failed

to rise. At the same time the urine record shows that diuresis was scanty. Almost the whole 10 gm. of salt was evidently taken up somewhere in the fluids or cells of the body. The rise of urea and creatinine in either edema fluid or blood might thus possibly be conceived as due to retarded excretion.

The blood-pressure, both systolic and diastolic, distinctly fell at the time of the increased plasma chloride concentration and also of the supposed increase of blood volume. Thereafter it rose nearly to the initial height. The blood-pressure in this patient was always low rather than high, and in cases of this sort it is a rule that increase of blood chloride or blood volume does not raise the blood-pressure.

Experiment V. Acid Administration. (Chart V.)

The patient drank 1 c.c. of concentrated hydrochloric acid mixed with water. No water was taken subsequently. Absorption may have been slow, as indicated by the lateness of the effects. The urinary acidity actually declined up to the sixth hour, then rose sharply. The CO_2 capacity of the plasma remained stationary for three hours, then fell to the sixth hour, and by the eighth hour had risen above the original level. The CO_2 capacity of the edema fluid for some reason rose during the first hour, then in general fell and remained lower than at the outset. The chlorides of the plasma changed relatively little, while the concentration in the edema fluid showed unexplained fluctuations. There was a curious rise of blood urea, but no urea analyses were performed upon the edema fluid. The plasma sugar exhibited a slight slow rise, while that in the edema fluid was practically unchanged.

Experiment VI. Bicarbonate Administration. (Chart VI.)

The fasting patient took 15 gm. of sodium bicarbonate dissolved and suspended in 50 c.c. of water. The bicarbonate concentration of the plasma rose markedly to the third hour, then remained practically constant. The concentration in the edema fluid fluctuated moderately up to the fourth hour, then remained constant. The result of the disproportionate rise in the plasma was that this

was much closer to the edema fluid in bicarbonate content at the close than at the beginning of the experiment. The chlorides for

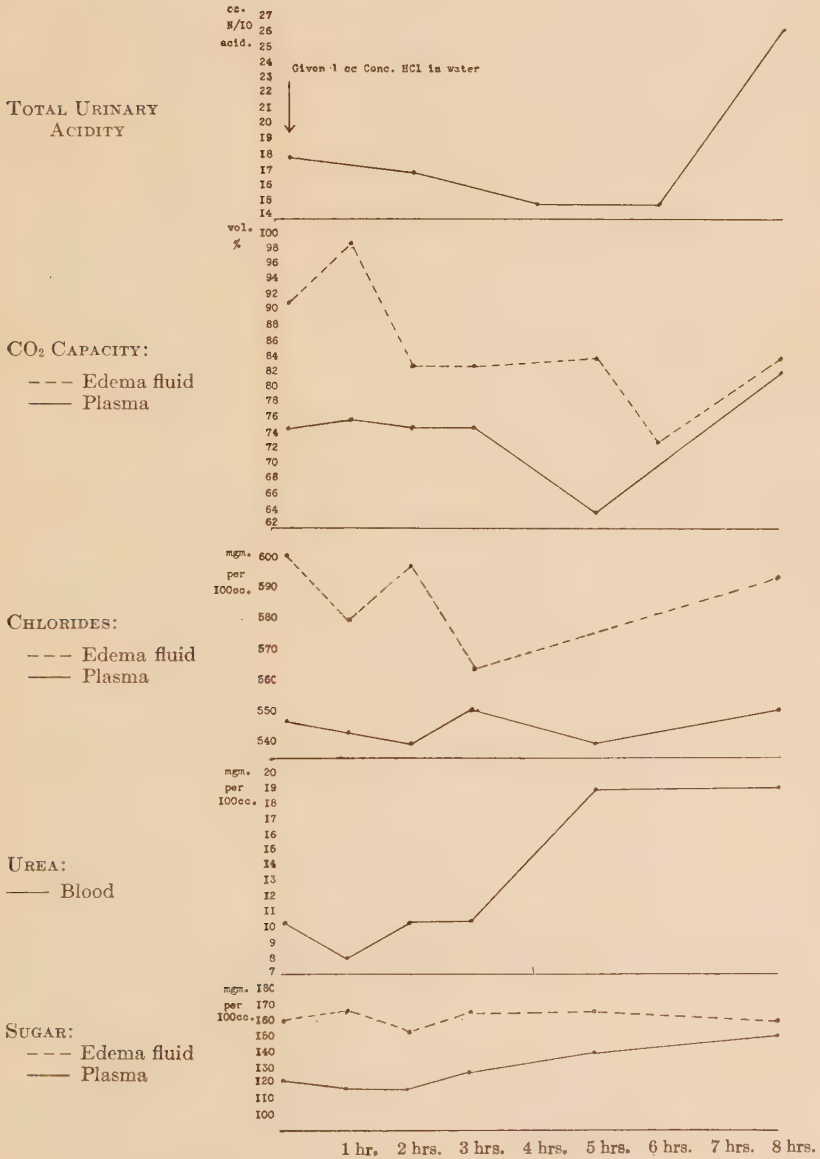

CHART V

some reason underwent a rise in the plasma but no important change in the edema fluid. Urea analyses were not performed upon the edema fluid but there was a moderate rise of concentration in the blood.

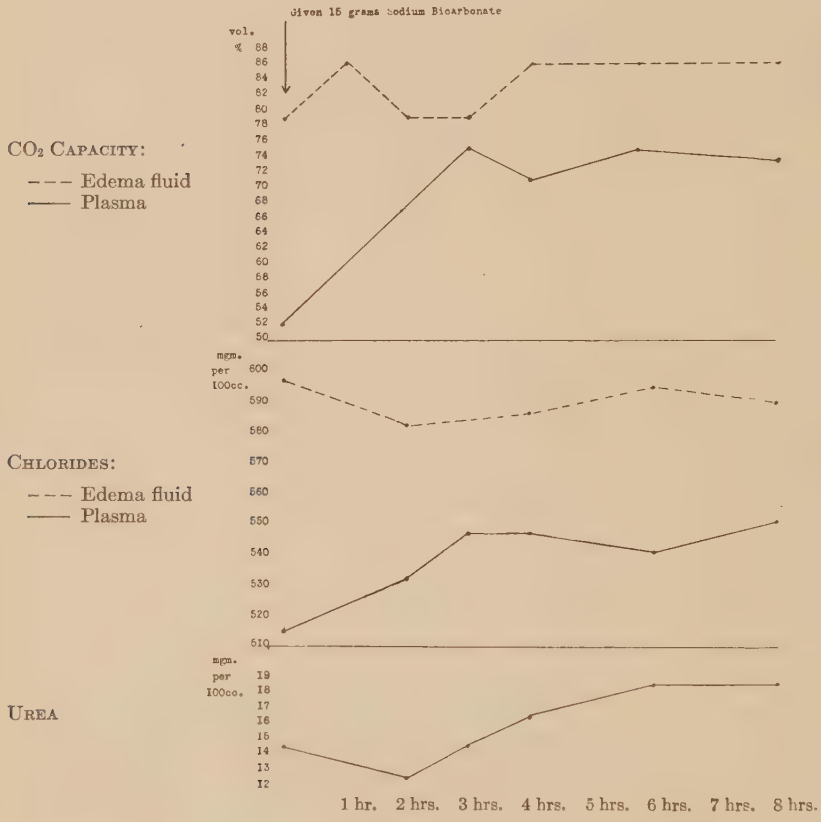

CHART VI

The principal point is that in this patient the rise of plasma bicarbonate did not indicate a corresponding enrichment of the rest of the body fluids.

III. Drugs and Exercise

A woman, aged eighty years, with long-standing neglected diabetes, moderate acidosis and advanced weakness and emaciation, exhibited on admission a marked anasarca, apparently due in part

TABLE III.—CASE OF DIABETES WITH EDEMA. PRELIMINARY PERIOD, AND ANALYSES OF BLOOD AND EDEMA FLUID AFTER DIGITALIS AND DIURETIN THERAPY.

	Time.	Fluid.	Urea.	NaCl.	Sugar.	CO^2 capacity.	Nitroprusside reaction.	Corpuscle volume, per cent.	Red blood cells, millions.	Remarks.
Apr. 17	P.M.	Blood	20	520	439	51.0	Slight +	42.4	4.0	Admitted; edema of ankles, legs and buttocks, with slight ascites.
		Edema	24	590	516	56.5	Heavy			
Apr. 21	P.M.	Blood	18	543	381	51.9	Slight	..	..	Digesting blood.
		Edema	14	583	237	62.3	Moderate +			
Apr. 23	..	Blood	..	535	453	..	Slight +	..	..	
		Edema	..	558	..	69.1	Moderate +			
Apr. 27	A.M.	Blood	22	535	381	55.7	Moderate			
		Edema	16	550	402	66.2	Moderate +			
May 1	A.M.	Blood	18	540	376	65.3	Slight	41.5		
		Edema	10	573	381	69.1	Slight +			
May 10	11.30	Blood	10	510	391	67.2	Faint	41.9	3.6	Before drinking water.
		Edema	16	535	391	77.7	Faint +	..	..	
May 10	1.20	Blood	13	515	329	73.9	Faint	38.3	3.8	Two hours after drinking 2500 c.c. distilled water.
		Edema	12	520	337	75.8	Faint +			
May 27	P.M.	Blood	24	550	263	78.7	Faint +	..	4.0	Course of digitalis started.
		Edema	25	535	241	78.7	Faint +	35.5		
May 28	A.M.	Blood	20	550	241	76.7	Very faint	38.4	3.8	
		Edema	20	530	241	76.7	Vaint +			
May 28	P.M.	Blood	22	510	268	79.6	0	34.2	3.3	
		Edema	18	535	273	82.5	Very faint			
May 29	A.M.	Blood	15	530	273	73.9	Faint	39.4	3.6	Edema decreased.
		Edema	14	530	302	76.7	Faint +			
May 29	P.M.	Blood	21	525	273	62.3	Faint +	36.2	3.3	Edema fluid albumin, 14.3 gm. per l.
		Edema	30	550	273	76.7	Moderate +			
May 30	A.M.	Blood	23	550	268	78.7	0	36.9	3.5	Edema decreased.
		Edema	23	540	308	72.9	Faint +			
May 31	A.M.	Blood	23	520	258	74.8	Very faint	35.5	3.4	Plasma albumin, 40 gm. per l; edema albumin, 10 gm. per l.
		Edema	20	525	296	84.4	Faint +			
June 1	P.M.	Edema	21	505	308					
June 2	P.M.	Blood	22	505	329	81.5	Faint +	37.2	3.6	Diuretin, grs. viii, t. i. d.
		Edema	21	525	308	77.7	Faint +			
June 3	A.M.	Blood	24	510	362	78.6	Faint	41.0	3.5	
		Edema	20	500	352	93.0	Heavy			
June 4	A.M.	Blood	20	..	345	85.5	.....	39.7	3.6	Edema much decreased, still persists; medication discontinued.
		Edema	..	..	..	80.5	.....			
June 6	A.M.	Blood	14	510	193	86.2	0	37.8		
		Edema	13	510	219	86.2	Faint			

to bicarbonate dosage and in part to cachexia. Treatment consisted in bed rest, fasting and low-calory salt-free diets, never above 50 gm. protein and 5 gm. carbohydrate, almost fat-free. No

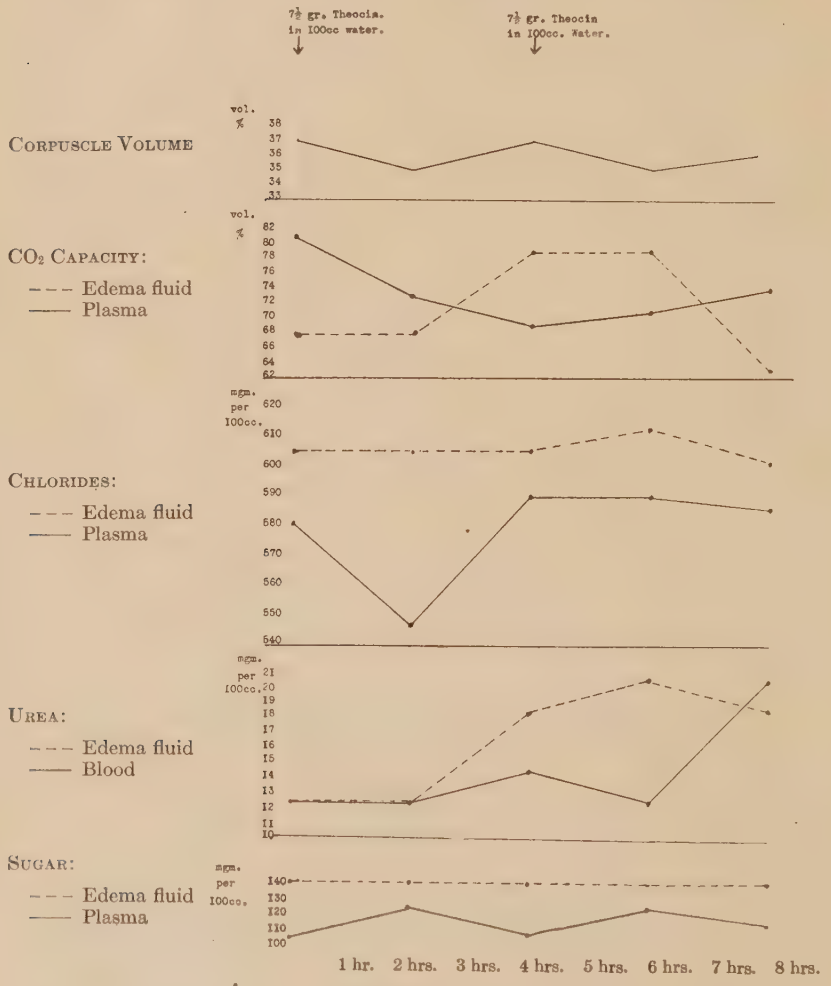

CHART VII

alkalies were given in the hospital, but there was a steady rise of the plasma bicarbonate as the acetone gradually cleared up. As this treatment, from April 17 to May 27, relieved the edema only

partially, drugs were tried and observations were made to learn whether these altered the distribution of substances in blood and edema fluid. Table III shows negative results in this respect with both digitalis and diuretin.

Chart VII.

Chart VII shows the results of a short theocin experiment upon the first mentioned patient with nephrosis. In general no positive result can be seen. The plasma chloride and bicarbonate concentration apparently fell after the first dose of theocin, but no such change followed the second dose. The urea rose in both blood and edema fluid. It should be added, however, that the results regarding diuresis were equally negative (Table IV).

TABLE IV.

Given 7½ grains theocin

Hour.	Volume, c.c.	Specific gravity.	Total NaCl, grams.
1	38	1028	0.022
2	0		
3	48	1028	0.092
4	0		
5	28	1028	0.026
6	0		
7	42	1034	0.024
8	0		
9	34	1024	0.032

The same patient was exercised to the limit of his strength, with a view to observing changes in the various substances under consideration, particularly the bicarbonate. When stair-climbing proved too exhausting, resort was had to mere forced breathing, following the work of Henderson and Haggard.[2] The CO_2 capacity of the plasma was thus on two occasions reduced from above 60 to approximately 52 volume per cent. No corresponding changes occurred in chlorides, urea or creatinine. The most interesting point was that the fall of plasma bicarbonate could not be accounted for by a migration of bicarbonate into the extravascular fluid. On the contrary the CO_2 capacity of the edema fluid remained stationary in the second experiment, while in the first one it actually fell in parallel with that of the plasma.

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1. Jacobson, A. Th. B., and Edwards, H.: Am. Jour. Med. Sc., 1920, clix, 833.
2. Henderson, Y., and Haggard, H. W.: Jour. Biol. Chem., 1918, xxxiii, 355.

DISCUSSION

Dr. Allen (closing) said that he did not want to make people believe that chlorides are to be blamed for every kind of condition. In diabetes there is high blood sugar, retinitis and cataract in the eye, a tendency to infection in all parts of the body, arteriosclerosis, gangrene, and various systemic disorders. One has to prevent the high blood sugar. Neverthless, many patients go on with glycosuria and high blood sugar and no complications. Likewise one may have high chlorides in the blood without complications. Still, there are disturbances with high chlorides and chlorides are the strongest osmotic agents; thus abnormal retention can cause many disorders: edema, arterial hypertension and some skin disorders. French authors attribute convulsions of eclampsia to high chlorides. The nervous disorders of epilepsy and the psychoses with edemas in cardiac conditions may be phenomena of chloride retention. One should study salt retention to see what it does and what it does not do, and discard mere speculations.

THE DUALISTIC CONCEPTION OF THE PROCESSES OF ANIMAL LIFE

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Animal life is manifested by an uninterrupted stream of various forms of perceptible activities, harmoniously performed by the various groups of the living tissues which enter into the make-up of the unit of a living organism. The multitude of the life phenomena may be reduced in a general way to three elements: motion, secretion and sensation. This classification may not be exhaustive but it is all sufficient for the object of this presentation. I wish, however, to emphasize that in most instances, if not in all, the perceptible activities are discontinuous; the activities alternate with periods of rest. The following examples will illustrate this point. Each cycle of a heart-beat is interrupted by a diastole when the heart muscle appears to be at rest. Or the peristaltic movements in one series of segments of the digestive tract, or of other tubes within the animal body, are accompanied by a more or less prolonged quietude of other segments of these tubes. Skeletal muscles contract at irregular intervals and only at the behest of some internal or external stimulus. Glands with external secretions functionate only at intervals and only as a result of certain provocations; for instance, the salivary glands, the digestive glands of the stomach and intestines prepare and empty their products in the corresponding cavities only when they are provoked by the entrance of food or by psychical stimuli. The same holds true for the sensory sphere; definite sensations are perceived only when certain receptive end-organs are affected by adequate stimuli.

Since the discovery of the circulation by Harvey, or perhaps, more correctly, since the discovery by Haller, that irritability is a

distinguishing property of all living tissues, physiologists have been busily engaged in discovering the causes for and the mechanisms of the various activities of the living animal organism. Two sets of nerves were discerned; one set carries impulses in the centripetal direction, from a receptive end-organ to the central nervous system or to prevertebral ganglia, and another set of nerves carries impulses from the central nervous system or from prevertebral ganglia to peripheral effective end-organs. The impulses transmitted by the centripetal nerves either cause well-defined sensations in various parts of the brain or cause organized nerve centers to send out reflexly impulses in centrifugal directions. The centrifugal nerves carry impulses either to motor mechanisms or to secreting glands.

Recently it was discovered that the circulation is carrying chemical stimulating substances from one part of the body to another without the intermediation of the nervous system. These substances which are manufactured by specific organs or tissues are now known as hormones.

Physiology in the past devoted its energies to the study of the causes and the mechanisms of the active part of living phenomena, and little or no attention was paid to the resting phase of these phenomena. On the surface of things this attitude would seem justified and logical. Only an action calls for an explanation, requires the discovery of a cause. Diminution of an action or its entire disappearance is readily explained by the reduction in the extent or intensity of the cause or by its complete elimination.

Are living tissues when they are inactive in a state of inanimateness? Seventy-five years ago a fact of first magnitude was discovered which permits, indeed compels one to look at life phenomena and at living tissues from a new angle. It is an undisputed fact that stimulation of the peripheral end of a motor nerve causes a contraction of the corresponding muscle which subsides with the discontinuation of the stimulation. The vagus nerve was considered as the motor nerve of the heart muscle. Now, in 1845, the brothers Weber discovered that stimulation of the peripheral end of a cut vagus causes the heart to stop in diastole. Let me add here that it was found later that during this standstill the heart muscle is more relaxed than during the normal diastole and that at the same

time its normal irritability or conductivity is diminished. Here was a new phenomenon, rest of a muscle is being brought about by an active cause, by a stimulus. The Webers designate the cardiac vagus as an inhibitory nerve. In the following half-dozen years numerous attempts were made to explain the cardiac standstill by all sorts of assumptions, but with no avail; inhibition came to stay. (Permit me to bring to your attention the following historical incident which is an interesting contribution to the psychology of investigators: A. W. Volkmann, a celebrated physiologist in his time and a brother-in-law of the Webers, investigated systematically the various nerves of the animal body as to their nature, whether they are sensory or motor nerves. While investigating the relations of the vagus nerve of frogs to the heart, he stimulated these nerves by turning a wheel of a faradic apparatus and counted the heart-beats. He found that before the stimulation the heart was beating twenty-six times per minute, while after the discontinuation of the stimulation the heart was beating thirty-one times per minute. From this he concluded that the vagus is a motor nerve of the heart muscle. He added: singularly enough the heart stopped beating during the time of stimulation. Four years later Volkmann discarded the entire value of his observation, under the assumption that muscles which contract spontaneously are not proper subjects for investigation. But three years later the Webers saw the same fact of the stoppage of the heart-beat during stimulation, and had the courage to pronounce it a new phenomenon in physiology.)

I may mention here that the inhibitory action of the vagus upon the heart was later shown to exist in human beings. Czermak succeeded in stopping his heart by compressing the vagi in the neck. On the other hand it was shown that the inhibitory nerve fibers of the vagi are moderately stimulated continuously in man and in certain animals by means of a center in the medulla which is in a state of tonus. The administration of atropin paralyzes the nerve endings of the inhibitory vagus and thus accelerates the heart-beats.

Is it logical to assume that the cardiac vagus demonstrates the only inhibitory phenomenon in the animal body? In the course of the three-quarters of a century which passed since the discovery

of the vagus action upon the heart, numerous inhibitory phenomena have been discovered. The time at my disposal is by far too short to attempt to enumerate all the new facts which bear upon this question. But I shall try to mention a few. In the first place I may mention one fact which the speaker was instrumental in discovering. Forty years ago I studied the physiology of deglutition. It was established that after the contraction of the mylohyoid muscle and the elevation of the larynx which characterize the initial act of swallowing a characteristic peristaltic movement runs down the esophagus and reaches the cardia in about six seconds. The question arose, What happens to this peristaltic wave in the esophagus when deglutitions were repeated every second or two? The answer was a surprise. After frequent swallows the peristaltic wave of the esophagus sets in only after the last swallow. This fact and other observations prove conclusively that in the complex reflex acts of deglutition, with each swallow an inhibitory impulse runs ahead of the impulse which causes the progress of the peristaltic wave in the esophagus. Animal experimentation demonstrated that both impulses run not in the periphery but in the center of deglutition. It was further discovered that during the act of deglutition the inhibitory impulse irradiates to neighboring centers within the medulla. It inhibits the tonus of the cardiac vagus, the vasomotor tonus and the activity of the respiratory center. These findings present a definite evidence that inhibition is an integral part of a normal function of the animal body.

Permit me here to make a side remark. Most of the physiologic experimentations have to be made on animals while they are under anesthesia. But since anesthesia suppresses the activities of the center of deglutition I had to perform these experiments on myself. It was certainly not a great pleasure to have for many hours two stomach tubes, with distended balloons at their end, in my pharynx and in the esophagus. The experiments were carried on in the physiological institute of the University of Berlin. One day Herr von Goslar, then the Minister of Education in the Prussian Government, came to see these experiments. A few days later we learned the purpose of his errand. The Junker party introduced in the Prussian Diet a law to suppress animal experimentation. In reply

to the old challenge that if physiologists are so anxious to contribute to science, why did they not make the experiments upon themselves, von Goslar told them what he saw in the physiologic laboratory, adding that he was sure that among the gentlemen of the extreme Right, with all their reputed courage, there was no one who would be willing to perform such experiments upon himself for money or glory. That finished the vicious Junker attack upon the medical sciences. I tell this story because there are many hysteric people imbued with the same Junker spirit of enmity against the medical sciences.

The existence of inhibition was discovered in most of the manifestations of life. Most interesting are the findings in which the presence of the inhibitory factor facilitates the prompt functioning of a physiologic mechanism. In the past twenty-five years Sherrington studied many instances in which simultaneously with the contraction of one group of muscles the corresponding antagonistic group is inhibited. For instance, the contraction of the flexor group is accompanied by an inhibition of the extensor group of muscles, and *vice versa*, or the contraction of an adductor group is accompanied by a simultaneous inhibition of the corresponding abductor groups, and *vice versa*. Sherrington designated this mechanism as *reciprocal innervation*. In 1883 I called attention to the existence of the mechanism of reciprocal innervation in the respiratory function. During inspiration the inspiratory muscles contract while the expiratory muscles relax, and *vice versa*. Recent experiments on fowls by Dr. Arthur Meyer and myself brought out a striking illustration. Fowls have no diaphragm. The inspiration is caused by the contraction of the intercostal muscles. The expiration is accomplished by the contraction of the abdominal muscles. In these experiments the inspiratory muscles and the internal oblique muscle of the abdomen were prepared to record separately on a revolving smoked drum. It was very instructive to find that on stimulating the central end of one vagus the thorax was raised to an inspiratory phase, while the expiratory internal oblique muscle became relaxed. But the reciprocal innervation is only a part of a general law which I termed the Law of Antagonistic Innervation. As has been mentioned before, in the act of deglutition the lower part

of the esophagus relaxes while the upper part contracts. Bayliss and Starling found that a stimulus applied to the intestine causes a contraction above and a relaxation below the point of stimulation. Joseph and I found that during a contraction of the pylorus a relaxation of the duodenum takes place. Cannon and Lyman observed that during the contraction of the ileum the iliocecal valve relaxes. The relaxation of all these segments of the digestive canal, which takes place simultaneously with the contractions of the segments above them, means that the lower part is inhibited, relaxed, in order that it may not offer an obstacle to the progress of the contents propelled forward by the contractions of the segments above. But in these instances there is no reciprocity. The general law means that in each motor function an inhibitory factor is involved which removes any resistance that may be offered by antagonists.

The detection of inhibitory phenomena is surrounded with great difficulties because only in exceptional instances can they be reached by separate nerves. But here again the extrinsic nervous mechanism of the heart offered a helping hand. About fifty odd years ago Ludwig and Bakst discovered fibers in the sympathetic nervous system which are antagonistic to the inhibitory nerves of the vagus, that is, the stimulation of these nerves accelerates the heart beats and augments the systolic contraction. During this effect the irritability and conductivity of the heart muscle is increased. This bundle of nerves is known as accelerators. There are certain characteristic differences between the inhibitory nerves of the vagus and the accelerators. Thus the vagus has only a short latent period while the accelerators have a very long latent period—that is, the nerves have to be stimulated a long time before they develop their effect upon the heart. Furthermore the vagus has only a short after-effect while the accelerators have a very long after-effect —that is, after discontinuation of the stimulation the accelerating effect may continue for a minute and longer. Now if both kinds of nerve fibers are stimulated simultaneously, interesting phenomena make their appearance. During the stimulation practically no other effect is recognized but the inhibition of the heart-beats, but quite soon after discontinuation of the stimulus the heart starts beating at a rate as if there had been no other stimulation but that

of the accelerator nerves. That means that although during the simultaneous stimulation the accelerator seemed to exert no influence, the effect upon that nerve was merely covered but not annihilated, and it exhibited this influence after discontinuation of the stimulation in a manner as if it had been stimulated all alone. These facts helped to demonstrate the presence of accelerator fibers in the vagus nerve of the frog. Besides the differences mentioned there are other conditions which distinguish the two kinds of nerve fibers. They differ, for instance, in fatigability and in their behavior toward the effects of temperature.

Now the overwhelming immediate effect of the inhibitory nerves and the long after-effect of the accelerator nerves is not peculiar to the inhibitory or the accelerating side of these nerves. This can be seen in the effect of the chorda tympani and sympathetic nerves to the bloodvessels of the salivary glands. The bloodvessels in general are under the influence of peripheral antagonistic nerves, nerves the stimulation of which causes a contraction of the bloodvessels, and others the stimulation of which causes a dilatation of the bloodvessels, vasoconstrictors, and vasodilators. The vasodilators are considered as vascular inhibitory nerves. Now the chorda tympani nerve, which causes a dilatation of the bloodvessels of the submaxillary salivary glands, possesses a long after-effect, and the sympathetic nerve which causes a constriction of these bloodvessels has only a very short after-effect. When both sets of nerves are stimulated simultaneously, during stimulation only a vasoconstriction can be noticed, but after cessation of the stimulus a long-lasting, strong, vasodilatation makes its appearance. In contrast to the conditions found in the extrinsic nerves of the heart, here the vasoconstrictor, which may be compared with the accelerator, exerts an overwhelming effect during stimulation, while the chorda, the inhibitory nerve, possesses the long after-effect which comes to the fore after discontinuation of the stimulus.

Dr. Githens and I recently found in the nose-licking reflex a clear example of the role which the overwhelming effect of one set of nerves and the after-effect of the antagonistic set of nerves may play in the mechanism of some reflexes. We first found that a certain procedure which leads to mechanical anesthesia abolishes completely

all the sensations, leaving all the reflexes intact. Using this method of anesthesia, we discovered the nose-licking reflex. The tip end of the nose and the anterior part of the septum could be quite intensely compressed by means of a hemostatic forceps without producing any effect. But immediately on removal of the forceps the animal started licking its nose, which lasted a few seconds. Evidently the pressure stimulated two sets of afferent nerves, one set which would cause the licking reflex and the other set which inhibits this reflex. During the pressure the inhibitory nerves prevailed, but after removal of the stimulus caused by pressure, the long after-effect of the antagonistic nerves was permitted to become manifest and the nose-licking made its appearance.

As seen above, the overwhelming effect of one set of nerves upon the antagonists, and the long after-effect of another set of nerves, are not exclusive properties of either inhibitory nerves or nerves of action. Nor do we need to expect that in all instances each of these properties or both are so extreme as they were found in the examples cited. We may, for instance, assume that in the contraction of the skeletal muscle of vertebrates there are inhibitory and motor impulses simultaneously at work. The motor impulses may be indeed overwhelming during the indirect stimulation of the motor nerve or direct stimulation of the muscle. But after cessation of the stimulus there is a moderately long after-effect of the inhibitory impulse so as to cause a rapid relaxation of the contraction of the muscle. The direct or indirect stimulation of a vertebrate striated muscle does not offer undisputed evidence of the presence of inhibitory impulses through the motor nerves or in the muscle substance itself. But veratrinized muscles of frogs show a very slow relaxation after a contraction caused by direct or indirect stimulation. Now, Biedermann found that when a galvanic current has been applied to the muscle in this tonic state there was a rapid relaxation around the anode with the making of the current and a moderate relaxation around the cathode at the breaking of the current. Apparently the making and the breaking of a galvanic current is capable of inhibiting the tonic state of the muscle. As the same results were also obtained in curarized muscles the experiment demonstrates that the muscle tissue itself is capable of responding with an

inhibitory reaction. Highly interesting are the studies of Biedermann on the claw of the crawfish. When the abductor was divided and the nerve of the claw was stimulated it was found that a moderate stimulus caused a relaxation of the tonically contracted adductor, while a stronger stimulus caused its contraction; but when the adductor was cut and the nerve stimulated, the abductor muscle contracted with a moderate and relaxed with a strong stimulus. When each muscle was separately connected with a lever graphically marking their movements, and the stimulation of the nerve was gradually increased, it was found that the first effect was that of contraction of the abductor; next came the relaxation of the adductor; then followed the contraction of the adductor, and about simultaneously with it the relaxation of the abductor. These experiments show that each muscle is provided with inhibitory and motor nerves but that in the abductor it is the motor nerve which is most sensitive, while in the adductor it is the inhibitory nerve. The result is that a stimulus which is sufficient to contract the adductor keeps the abductor relaxed, and that a stimulus which causes the contraction of the abductor causes directly the relaxation of its antagonist. This is a beautiful example of Sherrington's reciprocal innervation. These experiments show that inhibitory effects may be discovered by the use of different intensities of stimulations. Another differentiating point is the time needed for the degeneration of nerves after they are cut. For instance, vasoconstrictors degenerate about four days after their section, while it takes ten days or more for the degeneration of vasodilators.

No doubt a great many more ways and means will be found to demonstrate the presence of inhibitory phenomena in the tissues and functions and the mode of their action in the various processes of life. But even as the matter stands today, with numerous well established facts at our disposal, we are entitled to insist upon the assumption that inhibition is an effective factor in all processes of life. We must keep in mind that the results as we have them today were attained in uphill work, that the attitude of many physiologists is generally inimical to admission of the presence of inhibitory phenomena, and that each new fact in this line had to struggle with various interpretations.

Before coming to the conclusion, I wish to quote here the most striking statement of Charles Bell made nearly a century ago. "The nerves have been considered so generally as instruments for stimulating the muscles, without thought of their acting in the opposite capacity, that some additional illustration may be necessary here. Through the nerves is established the connection between the muscles, not only that connection by which muscles combine to one effort, but also that relation between the classes of muscles by which the one relaxes and the other contracts. I appended a weight to a tendon of an extensor muscle which gently strengthened it and drew out the muscle; and I found that the contraction of the opponent flexor was attended with a descent of the weight, which indicated the relaxation of the extensor. To establish this connection between two classes of muscles whether they be grouped near together, as in the limbs, or scattered widely as the muscles of respiration, there must be particular and appropriate nerves to form this double bond, to cause them to conspire in relaxation as well as to combine in contraction. If such a relaxation be established, through the distribution of the nerves between the muscles of the eyelids and the superior oblique muscles of the eyeball, the one will relax while the other contracts."

Permit me now to formulate the dualistic conception of the processes of animal life. Irritability means the property of living animal tissues to react with a change in their state to a proper stimulus. The change may be two-fold: it may consist in an excitation, in an increase of activity; or it may consist in an inhibition, in a greater or less decrease in activity. Tissues and organs in a state of inhibition are as much in a living state as when they are in a state of excitation or activity. In a state of activity living material is used up (catabolism). In a state of inhibition living material is replenished (anabolism). Each and every state of life of plain tissue or of complex functions is a resultant of the combination of the two antagonistic factors, excitation and inhibition. In a state of utmost rest the factor of inhibition prevails greatly. But there is still a sufficient remnant of the factor of excitation to permit the tissues or the functions to remain in a state of tonus, of dormant life. On the other hand, in a state of extreme excitation there is still a

remnant of the factor of inhibition which thus prevents the excitation from consuming the living material which is indispensable to the life of the involved tissues.

Besides its indispensable value to the anabolic processes, inhibition is of importance to the prompt and proper activities of functions by elimination of simultaneous activities of elements directly antagonistic to the success of that function. It is also valuable to the economy of life by preventing the wasting of energies of living neighboring cells which are not needed for the performance of the specific function but are merely stimulated by irradiation of the exciting impulse from the chief focus.

SUBSTERNAL GOITER, WITH PRESSURE SYMPTOMS

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Summary. Female, aged sixty-four years, suffering from goiter, with symptoms of hyperthyroidism. Enlargement of the thyroid gland above the sternum very marked. The tumor also extended below the sternum and by pressure on the right phrenic nerve produced paralysis of the right side of the diaphragm and by pressure on the recurrent laryngeal nerve produced partial paralysis of the right vocal cord; it also displaced the heart toward the right side, producing a loud systolic murmur, with its intensity at the apex and a marked myocardial insufficiency.

Treatment. Roentgen ray, rest and medication.

Result. A fairly satisfactory recovery, the paralysis of the right diaphragm and right vocal cord remaining.

April 10, 1917. *Personal History.* Thirty-three years ago the thyroid gland began to enlarge and it has been enlarged ever since, but the patient has never had any symptoms referable to this condition. In 1916 I found pus in her urine, which readily yielded to treatment with urotropin and benzoate of soda. In the winter of 1917 pus was again found in her urine and disappeared under the same treatment.

December 1. The patient's present illness began during the summer of 1917, while at her summer home at the seashore. During August of this year she suffered from mental depression and shortness of breath. Early in September she consulted a physician, who found that she had a well-marked cardiac murmur and that her urine contained pus.

About the middle of October she was taken to New York and placed under the care of a physician, where she remained until her

return to Cincinnati on November 29, 1917. Her physician in New York reported that she had dyspnea on exertion, a well-marked systolic heart murmur, a blood-pressure of 148–74, a sterile blood culture and a negative Wassermann. On October 22 a blood examination showed hemoglobin 85 per cent. red blood cells 5,400,000, white blood cells 5000, polymorphonuclears 41, lymphocytes 54, eosinophiles 5. The urine examined on October 22 and November 12 contained no pus, and except for a very faint trace of albumin was negative. The patient was kept off her feet and in bed the greater part of the time she was in New York, and during this time she improved very materially. The cardiac dulness decreased.

On sending the patient to Cincinnati her physician wrote: "I feel that Mrs. Blank has for a basis of her cardiac changes a mild hyperthyroidism. She has had from time to time, in addition to the goiter, the following clinical evidence to substantiate this view: (1) Instability of pulse and a marked tendency to develop tachycardia; (2) flushing; (3) tremors."

November 30 I saw the patient at her home, twenty-four hours after her arrival from New York. She had been in bed during that time; she had symptoms of mild hyperthyroidism, a loud systolic murmur was heard most distinctly near the apex of the heart, which was transmitted into the axillary region, and was also heard very distinctly in the direction of the sternum, extending quite far up along the sternal line over the arch of the aorta. No diastolic murmur was heard. There was a dull area beneath the manubrium continuous with the cardiac dulness; the latter was increased downward and outward.

The left lung appeared normal but the lower border of the right lung upon percussion and auscultation did not appear to extend below the 7th or 8th rib posteriorly and the 4th rib anteriorly. Vocal resonance and fremitus were diminished or absent over the lower portion of the right chest. The vesicular sounds over the whole right lung were less distinct than over the left.

December 6, Dr. Samuel Iglauer, in consultation, found the left vocal cord paralyzed, and the inference was that this paralysis was produced by pressure from some substernal growth or from an aneurysm of the aorta.

A roentgen-ray examination made at this time was as follows: The stereoscopic roentgen-ray plates of the chest showed an opaque shadow beginning just above the arch of the aorta, extending up into the neck, where it became lost in the shadows of the deeper structures. This shadow extended about two inches to both sides of the sternal line. The arch of the aorta on its curve on the left side showed a number of dense shadows simulating calcareous deposits. The lower right side of the chest was opaque. The opacity extended posteriorly from below upward as high as the 8th rib and anteriorly as high as the 4th rib. The line of this shadow was straight and was evidently the lower border of the diaphragm. The fluoroscopic examination showed the same shadow in the same position, with no apparent movement of the diaphragm on the right side. The heart shadow appeared normal in size and pushed slightly to the left.

The roentgen-ray films of the teeth showed no root abscesses.

A blood examination showed hemoglobin 85 per cent., red blood cells 5,000,000, white blood cells 5200, lymphocytes 37 per cent., large mononuclear leukocytes 7.66 per cent., polymorphonuclear neutrophiles 52.66 per cent., eosinophiles 1.3 per cent., mast cells 1 per cent., myelocytes 0.0, Tuerck's irritation forms 0.3 per cent.

At this time, in addition to the diagnosis of enlarged thyroid with hyperthyroidism, it was our belief that that portion of the enlarged thyroid gland extending beneath the sternum pressed upon the recurrent laryngeal nerve, producing paralysis of the vocal cord, and also pressed upon the right phrenic nerve, producing paralysis of the diaphragm.

This patient was seen in consultation by Dr. Roger Morris and Dr. Max Dreyfoos on December 17, and on January 26, 1918. She was also seen on January 28, 1918, by Dr. James B. Herrick, of Chicago.

The physical findings and diagnosis as above recorded were confirmed by the consultants, and it was decided to seek surgical advice with reference to the advisability of a surgical operation.

It was the opinion of myself and all the medical men who had studied this case that it was not advisable to attempt the removal of the substernal thyroid, which was producing the pressure symptoms.

During the last week of February, 1918, the patient was taken to Chicago for medical and surgical advice. She returned to Cincinnati in about ten days, with medical and surgical opinions that it was not advisable to attempt an operation, and also with the advice that the medical treatment which she had had before going to Chicago should be continued.

At this time the prognosis was considered very bad by all the physicians and surgeons who had seen her. On her return to Cincinnati the treatment which she had received from the time she came under my observation was continued, and the remarkable improvement in her physical condition which has resulted I think justifies the clinical report here given.

TREATMENT. On December 1, 1917, when the patient first came under my observation, she was given 15 drops of tincture of digitalis three times a day. From that date to the present, covering a period of two years and four months, she has continued to take digitalis, omitting it for only short periods of time. At the present time she is taking 5 drops of the tincture twice a day, six days in the week. The dose has been gradually diminished and has been omitted occasionally for short periods. During nearly all of this time she has taken a capsule containing $2\frac{1}{2}$ grains of the neutral bromide of quinin, 1 grain of extract of ergot and $\frac{1}{30}$ grain of extract of belladonna.[1] This capsule was given three times a day for a long period of time, and throughout the two years and four months it has been taken almost continuously. During the past year she has taken two of these capsules per day. At rare intervals this treatment has been interrupted for a period of a few weeks.

In addition to the above treatment the patient took deep roentgen-ray treatments over the thyroid gland, given from two areas in the front and two in the back, never giving more than two areas at one time. These treatments, fifteen in all, were given by Dr. William M. Doughty on the following dates:

1918—January 4 and 15; March 5, 15 and 29; April 12 and 26; May 17; June 8; November 8; December 2.

1919—January 7; April 15; May 20; June 9.

[1] The above prescription was a favorite one of the late Dr. Frederick Forchheimer, of Cincinnati.

These treatments were all filtered through 4 mm. of aluminum.

When the patient came under my observation, December 1, 1917, she was practically confined to her room, spending most of the time in bed or upon a couch. Even the slight exertion of walking about the room produced shortness of breath and increased rapidity of heart action. During this time she was occasionally carried up and down stairs, and some months later was strong enough to take automobile drives. After four or five months of treatment her heart had sufficiently recovered for her to walk up and down stairs once a day. She has steadily improved in strength, so that at the present time she leads practically a normal life and presents the appearance of being in perfect health.

The physical signs so far as the lungs are concerned persist. The right diaphragm is in the same position as above described. An examination of the heart still shows a systolic murmur, which is loudest at the apex. This murmur, however, is now soft and very much diminished in intensity, and in the range of its transmission. It is my belief that at the present time the shortness of breath, still experienced after taking long walks, is due rather to the diminished lung capacity of the right lung than to any cardiac weakness.

The patient has not had a roentgen-ray treatment for nearly a year, and for more than a year there has not been any evidence of hyperthyroidism.

OBSERVATIONS ON THE BEHAVIOR OF DIPHTHERIA BACILLI IN WHOLE COAGULABLE BLOOD, WITH A COMPARISON OF THE RESULTS OF THE TESTS FOR BACTERICIDAL AND ANTITOXIC IMMUNITY IN THE SAME PERSONS

(ABSTRACT)

By SOLOMON SOLIS-COHEN, M.D., GEORGE D. HEIST, M.D.[1]
AND
MYER SOLIS-COHEN, M.D.
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(From the Jules E. Mastbaum Research Laboratory of the Jewish Hospital, Philadelphia.)

In previous communications[2] [3] we described a simple test which distinguishes *in vitro* animals that are susceptible to pneumococcic infection and those that are immune. We also applied the same test to distinguish between animals immune and susceptible to infection with globoid bodies; and by its means Matsunami and Kolmer[4] as well as ourselves were able to separate animals respectively susceptible and resistant to meningococcic infection.

[1] Dr. Heist, whose yet unpublished studies of the meningococcus showed his own blood to be lacking in resistance to that organism, died of cerebrospinal meningitis on August 8, 1920. Dr. Myer Solis-Cohen, who was associated with much of our work, has analyzed and summarized the laboratory notes made by Dr. Heist in the present study, and the results will be published with sufficient particularity of detail in an appropriate periodical. This is not the place for an appreciation of my beloved and greatly mourned pupil, friend and co-worker. S. S.-C.

[2] Heist, George D., Solis-Cohen, Solomon, and Solis-Cohen, Myer: The Bactericidal Action of Whole Blood, with a New Technic for its Determination, Jour. Immunol., iii, 261.

[3] Heist, George D., and Solis-Cohen, Solomon: The Bactericidal Action of Whole Blood of Rabbits Following Inoculations of Pneumococcus Bacterins, Jour. Immunol., 1919, iv, 147.

[4] The Relation of the Meningococcidal Activity of the Blood to Resistance to Virulent Meningococci, Jour. Immunol., 1918, iii, 201.

Matsunami and Kolmer[1] and we[2] have also with the same test ascertained the varying degrees of susceptibility to meningococcic infection in man. We have also been able similarly to demonstrate the gradual increase of immunity against pneumococcic infection and to measure the extent of immunity present during recovery and convalescence from pneumonia in man and following inoculation of killed pneumococci in rabbits. A part of that work was presented to this Association last year.[3] Block, Fowler and Pierce,[4] who tested our method with typhoid bacilli and the *Bacillus dysenteriæ* of Shiga, found it "the most dependable criterion of the active immunity of the animal."

In this test, whole, coagulable blood as it comes from the vessel is brought into contact with small numbers of bacteria adhering to the inner wall of a capillary tube. The tubes containing the bacteria and blood are sealed and placed in the incubator for twenty-four hours, when the contents are blown out on a slide. If the bacteria have not multiplied sufficiently to be seen on microscopic examination, the blood possesses some bactericidal power against that particular organism. If necessary, the observation may be confirmed by plating, as in our pneumonia work.

The *degree* of natural bactericidal immunity or artificial immunization may be approximated in either of two ways. One method is to incubate for *various periods of time* a series of capillary tubes, each containing a *standard number* of bacteria (*i. e.*, a given dilution), and to note the shortest time in which growth of the bacteria can be detected. In the other method, which we have employed in most instances hitherto reported, a series of capillary tubes containing *various numbers* of bacteria (*i. e.*, various dilutions) are incubated for a *standard period of time* (twenty-four hours), and note is made of the smallest number of bacteria (*i. e.*, the highest dilution) that shows growth in that time. Each organism has its optimum method.

[1] Loc. cit.

[2] Heist, George D., and Solis-Cohen, Solomon: The Virulence of Meningococci for Man and Human Susceptibility to Meningococcic Infection. (To be published.)

[3] Tr. Assn. Am. Phys., 1919, p. 109.

[4] Development of the Bactericidal Power of Whole Blood and Antibodies in Serum, Jour. Am. Med. Assn., 1920, lxxv, 915.

In relation to *diphtheria*, susceptible and immune persons are supposed to be distinguished accurately by the Schick reaction. It accordingly appeared that diphtheria would offer a good field for further study of the bactericidal power of whole blood against the etiologic organism. If the whole coagulable blood of immune species and individuals should prove bactericidal to the diphtheria bacillus, while the blood of susceptible species and individuals should lack bactericidal power, this would be an additional proof of the value of this test for immunity. On the other hand, the fact that immunity to diphtheria is chiefly antitoxic rather than bacteriolytic seemed to promise some interesting variations that might lead to new light as to the meaning and method of the reaction in whole blood.

The first step was to study the growth of diphtheria bacilli in blood, both *whole coagulable blood* and *defibrinated blood*. Their behavior was then observed in the whole coagulable blood of certain animals, including the guinea-pig, rat, mouse and rabbit—in each instance using a number of animals of different ages and sizes—and in the defibrinated blood of these species and of the steer. Observations were made likewise upon the growth of diphtheria bacilli in the whole coagulable blood of human beings (including one who had recovered from diphtheria some years previously), and particularly in those reacting positively and in those reacting negatively to the Schick test.

The whole and defibrinated blood of all the lower animals tested, with the exception of the *rat*, failed to inhibit the growth of diphtheria bacilli. The *whole blood* of the rat proved bactericidal; its *defibrinated blood* did not.

The endeavor was then made to determine whether the whole blood of every animal of a definite species immune to infection with the diphtheria bacillus possesses at all times bactericidal power against *Bacillus diphtheriæ* and whether all members of a definite susceptible species always lack this power. The *rat* was selected as the immune animal and the *guinea-pig* as the susceptible animal. We found that with scarcely any exception diphtheria bacilli seeded in the whole blood of rats grew feebly or not at all, while those seeded in the whole blood of guinea-pigs grew vigorously.

The conditions under which the diphtheria bacilli were *cultivated*

were varied in order to find, if possible, the most favorable ones. Cultures were made on Loeffler's medium, on blood agar, on blood broth and on plain broth, and suspended variously in plain broth, in toxin broth (of both high and low potency) and in serum broth. The quantity of water of condensation was varied and the dilutions of the cultures were made with plain broth, with toxin broth, with toxin, with antitoxin, with toxin-antitoxin mixture and with normal salt solution. The objective in using toxin and toxin broth was to restrain the phagocytic action of the leukocytes, while antitoxin was employed for an opposite end—to neutralize the toxin of the organisms and thus afford full opportunity for phagocytosis. All the suspensions gave about equal results under like conditions, but normal salt solution seemed to be the best diluent for routine work. Drying had little or no influence on the behavior of the organisms.

The *time* element was also studied. The organisms were grown for varying periods in the different media before washing off, and cultures mixed with the blood of guinea-pigs, of rats and of Schick-positive and Schick-negative human beings, were incubated for different lengths of time.

The results varied but little. Four strains of *Bacillus diphtheriæ* were employed: (*a*) Park and Williams No. 8, a well-known organism of known virulence still producing toxin; (*b*) a freshly isolated strain from a patient in the Jewish Hospital; and (*c*) and (*d*) two freshly isolated strains from the Laboratory of the Philadelphia Bureau of Health. Strains *b*, *c* and *d* each killed a guinea-pig in twenty-four hours.

The tests on *human blood* did not show, as to individuals, any parallelism between original or acquired antitoxic immunity as demonstrated by the Schick test, and the original immunity of the rat as demonstrated by the bactericidal test; although there is some indication of a low degree of kinship between these phenomena when the results in large groups of Schick-positives and Schick-negatives are compared. This may briefly be illustrated:

First may be reported certain observations on a small group of *adults*. A number of experiments were made with the blood of one of us (G. D. H.) and the blood of the laboratory assistant (L. S. B.), using Gaffsky's scale. But, paradoxically, the one which

gave a positive Schick reaction (G. D. H.) had high bactericidal power against the *Bacillus diphtheriæ,* while the other (L. S. B.), which gave a negative Schick reaction, had low bactericidal power against that organism. The individual who had recovered from diphtheria (L. J.) gave likewise a negative Schick reaction, with low bactericidal power against *Bacillus diphtheriæ.* It further seemed that there was a periodicity in the degree of bactericidal power in the blood of the one (G. D. H.) possessing bactericidal immunity with a positive Schick reaction; the results in tests made on nineteen different days over a period of thirty-six days, showing certain variations in resistance from day to day. But not all persons were thus paradoxic in response to the two tests. Other adults showed more or less bactericidal power with negative Schick reaction, and still others positive Schick reaction together with absence of notable bactericidal power. In fine, there was both individual correspondence and individual divergence in the two responses.

Schick tests were then made on 176 *children,* whose whole blood was also tested for bactericidal power. The results were in general the same as those in adults. There was neither uniform correspondence nor uniform divergence between bactericidal immunity and antitoxic immunity. In a child giving the positive Schick reaction the blood might be bactericidal to the *Bacillus diphtheriæ,* while in a child giving a negative Schick reaction the blood might have low or no bactericidal power against this organism. In the whole number tested the correspondences and divergences were too nearly balanced to admit of a definite conclusion, if we exclude one group of 45 children tested in batches of 15 at a time within a few days. These showed 26 positive Schick reactions with low bactericidal power against 6 positive Schick reactions with high bactericidal power, and 9 negative Schick reactions with fair bactericidal power against 4 negative Schick tests with low bactericidal power.

If this result may be accepted as an index, it would appear that among those giving positive Schick reactions there is a greater proportion of individuals with low bactericidal power than among those exhibiting a negative Schick reaction; and, conversely, a greater percentage of individuals having high bactericidal power among

those responding negatively to the Schick test than among those responding positively. In other words, a majority of these 45 children possessed or lacked bactericidal resistance and antitoxic immunity together, while a minority possessed one and lacked the other. But we are far from affirming this to be an universal rule; on the contrary, the greater number of observations thus far made is against it. Among the observations in progress and to be published later this feature is studied more fully and certain attendant circumstances noted. The present communication is to be considered merely as a preliminary note.

DISCUSSION

Dr. E. C. Rosenow, of Rochester, Minn., asked whether the blood and plate results agreed. Was there any coagulation of the blood in the tube which might have exerted influence that way?

Dr. S. Solis-Cohen, of Philadelphia, said that the work was developed to test out as many organisms as possible, or to determine what relation there was between the blood and resistance to different organisms. Work on meningococci and pneumococci had given corresponding results. The importance of the work was to test immunity in human beings to bacterial invasion, and to see if there was any relation between this and the bactericidal effect of the blood as studied in the test-tube. If this could be shown there would be a distinct advance. The criticism that the action was inhibitory and not bactericidal was probably true in part; but there was found to be a distinct bactericidal value which could be expressed either as time or number. If no growth occurred within a defined time, a large number of bacteria had been killed.

Dr. Rosenow asked how the plate culture was inoculated and how they got an even distribution.

Dr. Heist, Philadelphia, said that it was inoculated on the surface of the solid agar. He took a loopful with 5 c.c. of saline solution, shaking it up thoroughly, put it on the plate and spread it thoroughly with a glass rod. The blood was allowed to clot in a capillary glass tube. Clotting probably had an important bearing, as it gave the leukocytes some scaffolding, as it were, to work upon. In the diphtheria work phagocytosis was a very important factor, but there might be some other as well. Opsonins were probably present in the serum, but whole blood would be different from serum. Citrated blood would interfere with the test.

STUDIES OF THE ACID BASE EQUILIBRIUM IN DISEASE FROM THE POINT OF VIEW OF BLOOD GASES*

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I. Introduction. The problem of acidosis resolves itself into two fundamental questions: (1) In any given case is there an acidosis in the sense that the available alkali of the blood is diminished through the presence of an increase in non-volatile acid; (2) is there an acidosis in the sense of an actual change in blood reaction in the acid direction, of an increase, in other words, of the concentration of ionized hydrogen? In disease these conditions may occur alone or combined. To recognize each and to distinguish between them is of some clinical importance. Data concerning the former are abundant in the literature, data concerning the latter somewhat less so, and data showing the two simultaneously are scanty.

The question of available alkali of the blood in disease has been approached by a large number of investigators and by very divergent methods. Of the more recent work the following general types may be cited by way of illustration. I. Determination of titrable alkalinity of the blood after the manner of Sellards.[1] II. Determination of the carbon dioxide capacity of the serum by the method of Van Slyke.[2] III. Determination of the oxygen combining power of the blood at a given tension of oxygen as done by Barcroft.[3]

The question of the actual reaction of the blood in health and disease has also been approached in several ways. The reaction can be

* From the Medical Service of the Massachusetts General Hospital. This paper is Study No. 1 of a series of studies of the physiology and pathology of the blood from the Harvard Medical School and allied hospitals.

measured directly either electrometrically by the so-called gas chain of Hasselbalch[4] or by the use of indicators as employed by Sörenson[5] and more recently by Bayliss.[6] It can also be arrived at indirectly from the behavior of the oxygen dissociation curve of the blood, the determination of the degree of meionoxy of Barcroft.[3] Finally it may be calculated from the carbon dioxide dissociation curve provided that the arterial carbon dioxide tension or concentration is known. Hasselbalch[7] has published a formula for such calculation which is dependent upon the principle shown by L. J. Henderson[8] that the reaction of the blood is dependent chiefly upon the ratio of free carbonic acid to bicarbonate, which can be expressed by the formula

$$[\overset{+}{H}] = K \frac{[H_2CO_3]}{[BHCO_3]}$$

in which $[\overset{+}{H}]$ is the concentration of ionized hydrogen, $[H_2CO_3]$ the concentration of free carbonic acid and $[BHCO_3]$ the concentration of bicarbonates, and K a constant. The fraction

$$\frac{[H_2CO_3]}{[BHCO_3]}$$

ordinarily has a value of approximately $\frac{1}{20}$. Changes in this ratio it can easily be seen will denote changes in the $[\overset{+}{H}]$, that is, in blood reaction, while changes in the actual magnitude of the denominator will denote changes in available alkali of the blood and changes in the numerator, changes in carbon dioxide tension. Knowledge then of the two terms of the ratio in any given blood will tell us the two most fundamental facts of acidosis.

For clinical purposes the simplest way of arriving at the value of the ratio and of determining the actual magnitude of the two terms of the fraction is to secure the data necessary to plot the so-called "Carbon Dioxide Diagram of the Blood" of Haggard and Y. Henderson.[9] This diagram, which incidentally is essentially a graphic representation of L. J. Henderson's formula, consists in the carbon dioxide dissociation curve of the blood determined after the manner of Christiansen, Douglas and Haldane[10] with a mark upon it which denotes its intersection with the coördinate representing the tension or concentration of carbon dioxide in the arterial blood, this point being called the A point.

After a conversation with Professor Y. Henderson in January, 1920, we were greatly impressed with the lucidity of such diagrams in the interpretation of problems of acid base equilibrium, and we take pleasure in acknowledging that it was through his stimulation that we undertook the present research, which consists in the construction of such diagrams for the bloods of patients, for the purpose of determining the presence or absence of non-volatile acid in their blood, and of actual changes in their blood reaction.

The information to be gathered from the dissociation curve thus plotted with its A point, is as follows: In the first place the abscissæ in the diagram indicate the tension of carbon dioxide in the blood and therefore the concentration of dissolved carbonic acid, for it is well known that the concentration of carbonic acid in physical solution is directly proportional to its partial pressure or tension. The abscissa therefore is the numerator of the fraction in L. J. Henderson's formula, $[H_2CO_3]$. Secondly, the ordinates are indices of the denominator of the fraction or the concentration of bicarbonates in the blood $[BHCO_3]$, for although what is actually determined is the total carbonic acid of the blood, not only that in chemical combination as bicarbonate, but that in physical solution as well, yet since the latter is directly proportional to the tension it can be disregarded. Indeed Haggard and Henderson in their diagram by drawing a diagonal base line show directly the amount of carbon dioxide in physical solution and of that chemically combined. We have not used this method for in the majority of curves in the literature the total carbonic acid at any given tension has usually been plotted above a horizontal base line.

If now the abscissa represents dissolved carbonic acid concentration and the ordinate bicarbonate concentration, and if hydrogen ion concentration is dependent upon the ratio of these two to each other multiplied by a constant, then for any given point in the diagram a series of radii drawn through the zero point will indicate the magnitude of the hydrogen ion concentration. Also in any given arterial blood the position of the A point will show the reaction. As long as the value of the ratio $[H_2CO_3] : [BHCO_3]$ remains constant, though its actual terms may vary in magnitude, the A point will always fall on the same straight line drawn through the zero point. We have therefore drawn a diagonal, the line OC in Fig. 1, which

runs approximately through the A points of a number of normal bloods. Pathologic bloods, if their A points fall to the left of this line, will have a more alkaline, if to the right a less alkaline reaction than normal.

By the "Carbon Dioxide Diagram", then, we are informed first of the presence or the absence of acidosis in the sense of a changed blood reaction, and, secondly, we are informed of the presence or absence of non-volatile acid in the blood. This last is shown by the level of the dissociation curve. The effect of adding acid to the blood is to diminish its available alkali. This means that the dissociation curve will be moved downward, for the ordinate represents the concentration of blood bicarbonate. The two main facts of acidosis, then, are revealed by the diagram, through the position of the A point and the level of the curve.

II. Methods. There is nothing new in the methods we have made use of. Blood was drawn from an arm vein and placed in a tube containing some dry oxalate crystals. About 5 c.c. was placed in each of three tonometers which had previously been filled with mixtures of air and carbon dioxide of known tension. The type of tonometer used was that shown in Fig. 145 of Barcroft's book.[3] The tonometers were then placed in a brass cylinder filled with water at body temperature and slowly rotated in a horizontal position for ten minutes by a motor. This rotating bath was a copy of one which was in use in Barcroft's laboratory at Cambridge in 1913. After equilibration the carbon dioxide content of the blood from each tonometer was determined by means of Y. Henderson's blood gas apparatus.[11]

Three points in the dissociation curve were thus obtained and plotted as in Fig. 1. In the plot the ordinates represent the concentration of carbon dioxide of the blood in terms of volumes percentage, that is the contents as found by blood gas analysis. The abscissæ represent the tension of carbon dioxide in millimeters of mercury, that is the partial pressure of carbon dioxide in the equilibrating atmosphere. These points having been obtained for any given blood, the most probable curve was then drawn through them.

The next step in the construction of the "Carbon Dioxide Diagram" is the fixing of the arterial or A point. This can be done, of course, by finding either the concentration of carbon dioxide in the

arterial blood and its appropriate abscissa and the point where this intersects the curve, or by determining the tension of carbon dioxide in the arterial blood and finding the point where its ordinate intersects the curve. If both methods were used they would serve as a check upon each other.

The concentration of carbon dioxide in arterial blood we obtained by drawing samples under oil from the radial or brachial artery after the method of Stadie,[12] and then determining their carbon dioxide content with the Henderson apparatus. Direct determination of the tension of gases in the circulating blood has been done experimentally by Krogh[13] but could hardly be done satisfactorily with human beings. In the absence of lesions of the lungs or of disturbances of the circulation through the pulmonary circuit, however, it is safe to assume that the arterial blood so far as carbon dioxide is concerned is essentially in tension equilibrium with the alveolar air, as obtained by Haldane's method.[14]

In plotting the A point of our several curves we sometimes have made use of the carbon dioxide tension of the alveolar air, sometimes of the carbon dioxide content of the arterial blood. The method used in each instance is noted in Table I.

TABLE I.—DISSOCIATION CURVES: POINTS ACTUALLY DETERMINED.*

Curve 1.	M. N. W.'s blood, normal .	P CO_2	16.8	41.0	72.0	A point 37.5 mm.
		V CO_2	38.0	51.0	61.0	
Curve 2.	J. H. M.'s blood, normal . .	P CO^2	17.6	36.0	65.0	A point 40.6 mm.
		V CO_2	37.0	49.0	59.0	
Curve 3.	L. H.'s blood, diabetic acidosis	P CO_2	19.5	42.5	74.0	A point 14.6 mm.
		V CO_2	19.0	27.0	39.5	
Curve 4.	Same, one day later . . .	P CO_2	18.1	38.2	78.2	A point 20.5 mm.
		V CO_2	21.0	30.0	39.0	
Curve 5.	Same, three days after curve 4	P CO^2	18.5	42.5	67.0	A point 26.8 mm.
		V CO_2	lost	41.0	48.0	
Curve 6.	T. C.'s blood, renal acidosis .	P CO_2	17.9	32.5	67.0	A point 12. per cent.
		V CO_2	13.0	22.0	36.0	
Curve 7.	Same, next day after alkali .	P CO_2	18.5	35.4	69.5	A point 60. per cent.
		V CO_2	45.0	62.0	72.0	
Curve 8.	E. D.'s blood, influenza pneumonia	P CO_2	19.7	31.5	68.0	A point 57. per cent.
		V CO_2	38.0	44.0	61.0	
Curve 9.	G. A.'s blood, lobar pneumonia	P CO_2	18.5	32.5	67.5	A point 52. per cent.
		V CO_2	34.0	46.0	58.0	
Curve 10.	N. D.'s blood, bronchopneumonia	P CO_2	21.8	39.4	69.5	A point 68. per cent.
		V CO_2	50.0	58.0	70.0	
Curve 11.	E. H.'s blood, cerebral hemorrhage	P CO_2	22.0	34.5	69.2	A point 56. per cent.
		V CO_2	46.0	54.0	65.0	
Curve 12.	J. W. F.'s blood, myelogenous leukemia, secondary anemia	P CO_2	18.9	42.6	80.5	A point 40. mm.
		V CO_2	47.0	62.0	72.0	
Curve 13.	A. W. T.'s blood, secondary anemia	P CO_2	17.7	36.6	70.5	A point Lost.
		V CO_2	42.0	50.0	63.0	
Curve 14.	F. M.'s blood, idiopathic tetany	P CO_2	18.8	38.2	70.0	A point 58. per cent.
		V CO_2	43.0	53.0	66.0	
Curve 15.	J. B.'s blood, primary anemia	P CO_2	19.5	35.8	75.8	A point 70. per cent.
		V CO_2	55.0	69.0	74.0	

* P CO_2, partial pressure or tension of CO_2 in millimeters of Hg.
* V CO_2, CO_2 content in volume per cent.

III. Cases Studied. We determined in all fifteen dissociation curves. The points determined are all shown in Table I while the actual curves with their A points are shown in Fig. 1. Two of these curves were for the bloods of normal individuals, three were of the blood of a diabetic with acidosis, three were of the blood of pneumonia patients, two of anemias (one primary and one secondary), one of a patient with cerebral hemorrhage, one of a case of myelogenous leukemia and one of a case of idiopathic tetany.

Normal Individuals. As we stated earlier in interpreting the "Carbon Dioxide Diagram" one phase of the question is answered by the level of the dissociation curve. This being true it becomes necessary to discover the level of the normal curve. We have searched the literature for such curves and found several. In Fig. 1 a shaded zone is shown. Of the curves taken from the literature this zone will contain those of the bloods of Haldane,[10] of Hasselbalch,[7] of Parsons,[15] of Joffe,[16] of Liljestrand[17] and of Lindhard,[17] and also those of two of the present writers, J. H. M. and M. N. W. (curves Nos. 1 and 2). A similar zone has been published by Straub and Meier,[18] which is said to include 320 points of the bloods of 64 normal persons. The lower border of their zone falls within our zone, but their upper border is very much higher and so at variance with the work of other investigators that we are inclined to believe it incorrect. The A points of J. H. M.'s blood, of M. N. W.'s blood and of that of Haldane, Liljestrand and Lindhard all fall either on the OC line in Fig. 1, or at a distance on either side of it so slight that it would make a difference of not more than 0.02 in the P_h. The data for placing the A point of the other curves taken from the literature were not found in the several papers.

Diabetic Acidosis. Three curves (Nos. 3, 4 and 5) were obtained in the case of a boy with diabetic acidosis (L. H., Hospital No. 234768 W. M.).

The first of these curves (No. 3) was obtained on January 23, 1920. He had then just entered the hospital with a moderately severe diabetes mellitus, and with a considerable acetonemia. He was somewhat drowsy but not in coma. There was no noticeable hyperpnea and no subjective dyspnea. The low position of the curve on this day shows a very low combining power of the blood with carbon

dioxide and hence indicates the presence of a large quantity of non-volatile acid in the blood. Nevertheless the A point of this curve is practically on the OC line, which means presumably that his blood reaction was normal. He had, in other words, what has been called by Y. Henderson and others a compensated acidosis. He had acidosis in the sense of having abnormal acid present in his blood, but he had, by increasing his pulmonary ventilation and thereby reducing the tension of carbon dioxide in his alveolar air, so reduced the dissolved carbon dioxide of his blood that the normal value of the $[H_2CO_3] : [BHCO_3]$ ratio was preserved. Through his pulmonary response he had kept his blood reaction normal.

After this he was starved, but given water and salt freely, and on January 24 his dissociation curve had risen to the position of curve No. 4. The A point of this curve is slightly to the acid side of the OC line and may indicate that his compensation was not quite as good as it had been on the day before. It must be said, however, that as we approach the lower left hand corner of the diagram the position of the A point becomes less and less accurate. The experimental error in determining the carbon dioxide content by the method used is probably at least 1 per cent., and with low curves an error of 1 per cent. will make much more change in the P_h than it would with curves in the normal position. We should hesitate to say, then, that the A point of curve No. 4 really proved the presence of a decompensated acidosis. Curve No. 4 being higher in position than curve No. 3 shows that the patient had somewhat improved his supply of available blood alkali.

On January 27 curve No. 5 was obtained. This shows a very striking increase in available alkali and an A point on the OC line indicating perfect compensation.

Unfortunately no further observations were obtained with this patient, for he left the hospital against advice.

Nephritic Acidosis. We also had an opportunity to get two curves in the case of a man aged fifty-five years (T. C., Hospital No. 235223, W. M.), who was brought to the hospital with a very intense grade of hyperpnea. It proved to be impossible to measure his pulmonary ventilation, but from the general character of his breathing as compared with a similar case of hyperpnea reported by Means

and Rogers[19] it seemed probable that he was breathing 40 to 50 liters per minute.

His underlying malady was arteriosclerotic nephritis, but he had in addition an obstructing prostate and a double pyelonephritis. He was in a profound state of uremia and retention acidosis. The dissociation curve (curve No. 6) obtained the day he came in, February 19, 1920, had the lowest position of any in the series, indicating that the available alkali was very greatly reduced. Not only that, but the position of the A point of the curve definitely to the right of the OC line shows that in spite of his terrific hyperpnea, his respiratory response was insufficient to preserve his normal $[H_2CO_3]$: $[BHCO_3]$ ratio and he had an actual change in the reaction of his blood in the acid direction, a decompensated acidosis in other words. The actual shift in the P_h, as explained earlier, in this part of the diagram can only be roughly estimated, but it could not have been less than 0.2. His actual oxygen saturation on this day was 89.6 per cent. and his hemoglobin 69.3 per cent. (calculated from the oxygen capacity).

After the blood had been drawn for the first curve he was promptly started on large amounts of sodium bicarbonate intravenously and by rectum. A free flow of urine was also obtained by catheterization.

The next day, after he had had approximately 175 grams of sodium bicarbonate, there was a most extraordinary change. The hyperpnea had entirely gone and he was no longer drowsy. Curve No. 7 was obtained. The change in the curve is as extraordinary as that in his clinical condition. From being very low it has moved to a higher level than normal. On that day, then, his available alkali was greater than in normal individuals. Furthermore the A point had moved to the left side of the OC line to such a distance that we feel that he probably had, on that day, an actual shift in blood reaction in the alkaline direction. A large amount of fluid had been got into him and this was reflected in the hemoglobin, which had dropped to 51.1 per cent. He, moreover, no longer had arterial anoxemia, his arterial blood being 93.5 per cent. saturated.

The improvement of course was very transient, as he had practically no renal tissue worthy of the name. He became uremic and acidotic again, and died on February 23.

Pneumonia. A curve was obtained from each of three patients with pneumonia.

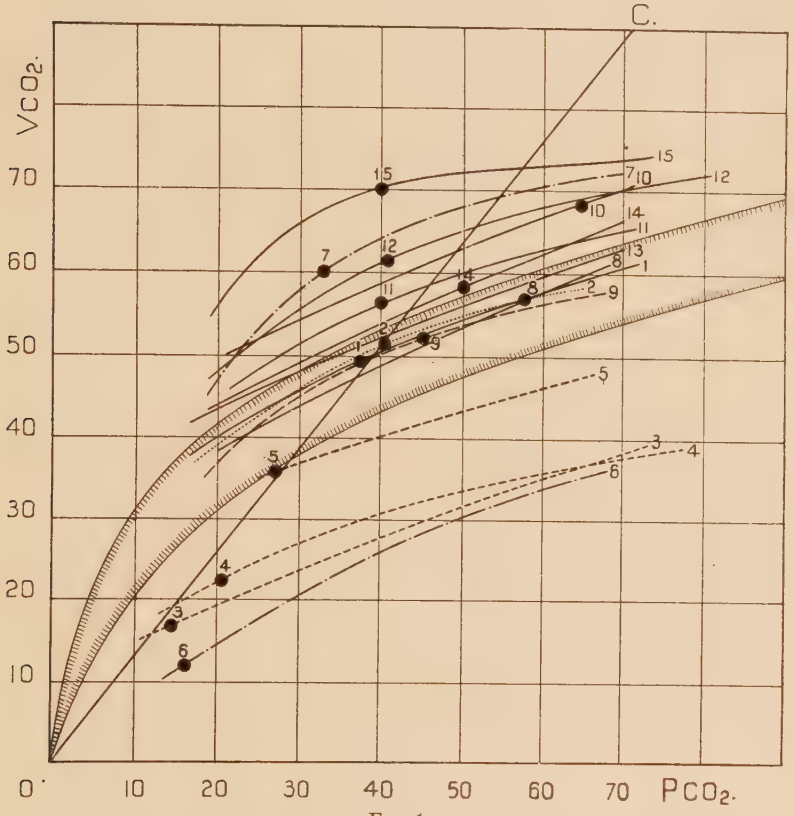

FIG. 1

"Carbon Dioxide Diagram," in health and disease. The ordinates represent carbon dioxide content of the blood in volumes per cent., the abscissæ tension of carbon dioxide in millimeters of mercury. The shaded zone indicates the area within which we believe the curves of normal bloods fall. The line *OC* represents the hydrogen ion concentration of normal blood. The arterial or *A* points are shown by black dots. The points in the several curves actually determined are shown in Table I. The several curves shown are as follows: 1, M.N.W., normal; 2, J.H.M., normal; 3, L.H., diabetic acidosis; 4, same, one day later; 5, same, three days after 4; 6, T.C., renal acidosis; 7, same, after alkali administration; 8, E.D., influenza pneumonia; 9, G.A., lobar pneumonia; 10, N.D., bronchopneumonia; 11, E.H., cerebral hemorrhage; 12, J.W.F., myelogenous leukemia, secondary anemia; 13, A.W.T., secondary anemia; 14, F.M., idiopathic tetany; 15, J.B., primary anemia.

The first of these (curve No. 8) was that of the blood of a man aged thirty-nine years with influenza pneumonia (E. D., Hospital No. 235143, E. M.). The curve was obtained on February 18, 1920. His influenza had begun on February 12 and his pneumonia on February 16. It was of the fulminating variety of influenza pneumonia. On the day the curve was obtained there were scattered areas of consolidation throughout both lungs. There was frothy bloody expectoration and a marked diffuse bronchitis. Respirations were rapid and shallow. He had a dull leaden cyanosis of the mucous membranes and finger tips. The striking thing about his diagram is that while the level of the curve is quite within the normal zone, the A point is far to the right of the OC line, indicating a definite shift in the blood reaction in the acid direction, equal roughly to a decrease of about 0.10 in the P_h. On the same day the oxygen saturation of this man's arterial blood was 59.3 per cent. and his hemoglobin 103.8 per cent. The arterial blood as drawn into a syringe was quite as dark as normal venous blood. He died on February 19. No autopsy was obtained.

The next diagram of pneumonia blood (curve No. 9) is that of a man aged fifty-nine years with true pneumococcus (Type 2A) lobar pneumonia (G. A., Hospital No. 234896, E. M.). The curve was obtained on February 11, 1920, his pneumonia having begun some two weeks before. He had on this day extensive double lobar pneumonia, the course of which had been progressively worse. His breathing was labored and grunting and he had marked cyanosis. About eight hours after the blood for the diagram was taken he died. No autopsy was obtained. His arterial oxygen saturation on February 11 was 74.5 per cent. and his hemoglobin 118 per cent. This man's curve, like the preceding one, is within the normal zone, the A point also being to the right of the OC line, but less strikingly so than in the case of E. D.'s blood.

The last pneumonia blood studied (curve No. 10) was that of a man aged forty-three years with postoperative bronchopneumonia. He also had pulmonary emphysema and chronic bronchitis (N. D., Hospital No. 235177, W. S.). He had an operation for gall-stones on February 21, 1920 and on February 22 his pneumonia began. The curve was obtained on February 25. On that day he had areas

of consolidation scattered through both lungs, many rales, deep cyanosis, and rapid grunting breathing. It is interesting to note that the level of his dissociation curve is above the normal zone, yet his A point like that of E. D. (curve No. 8) is well to the right of the OC line. His arterial oxygen saturation on February 25 was 86.3 per cent. and his hemoglobin 122 per cent. He made an uneventful recovery.

Blood Disease. The curve of three bloods of patients with blood disease were obtained. One of these (curve No. 12) was that of a man aged thirty-three years in a leukemic phase of myelogenous leukemia (J. W. F., Hospital No. 234688, E. M.); he likewise had a marked secondary anemia. The red cell count was 1,280,000, the white cell count 5600 and the hemoglobin 45 per cent. The interesting thing about his curve is that it throughout lies at a higher level than the upper border of the normal zone and that the A point lies to the left of the OC line.

The curve (No. 13) of a man aged forty-four years with secondary anemia of moderate grade (A. W. T., Hospital No. 235045, E.M.), whose red cell count was 3,248,000, white count 6600 and hemoglobin 73 per cent. also lay at a higher level than normal. Data for plotting the A point of this blood were unfortunately not obtained.

The diagram of the blood of a man aged fifty-six years (J. B., Hospital No. 235713, W. M.) with pernicious anemia (curve No. 15) showed a still higher position of the dissociation curve and an A point still further to the left than that of curve No. 12. This man's red cell count was 1,849,000, the white count 4000 and the hemoglobin 25 per cent.

Miscellanous Curves. One diagram (curve No. 11) was obtained in the case of a man aged fifty-eight years with a cerebral hemorrhage (E. H., Hospital No. 235387, W. M.). This showed a slightly higher level of the curve than did the normals, and an A point slightly to the left of the OC line.

The blood of a woman aged twenty-eight years with idiopathic tetany (F. M., Hospital No. 235679, E. M.) showed a curve just above the upper border of the normal zone (curve No. 14) and an A point slightly to the right of the OC line.

IV. Discussion. The interpretation of the results just presented is fraught with considerable difficulty. As we pointed out earlier, even the range of variation of the level of the carbon dioxide dissociation curve of normal blood is not known. The zone we have shown in Fig. 1, while it includes the curves determined for normal blood by a number of different observers, may perhaps not represent the true range. It may be either too wide or too narrow, or either or both of its borders may be too high or too low. It will require a large series of normal curves to determine correctly the limits of normal variation. Nevertheless the striking variations from the few normal curves available, that are shown by some of the pathological bloods here studied, it seems to us, are not without clinical interest.

Before passing to a discussion of the various trends of these variations, let us consider for a moment some of the pitfalls that lie in our way. In the first place what are the relative degrees of accuracy of the several procedures involved in the construction of the "Carbon Dioxide Diagrams." The shape and level of the dissociation curves we believe are substantially correct. The concentration of carbon dioxide in the blood by the method used should be accurate within 1 volume per cent.; that of carbon dioxide tension should certainly be accurate within less than 1 mm.

The position of the OC line, which we have drawn to represent the normal ratio of free carbonic acid to bicarbonate according to the calculations of Straub and Meier from Hasselbalch's formula, would indicate a P_h of approximately 7.35. The actual P_h of arterial blood as found by the gas chain is given by Michaelis[20] as 7.45. As already stated, the A point of the curves of Haldane's, Liljestrand's, Lindhard's, J. H. M.'s and M. N. W.'s blood fall either on the line, as we have drawn it, or at an insignificant distance from it.

About the accuracy of the position of the A points of the several curves we must speak with less assurance. As has already been said, two ways of plotting this point were used. Both these methods are open to criticism. The plotting of the A point from the carbon dioxide tension of the alveolar air would be satisfactory provided, first, that accurate samples of arterial pulmonary air could always be secured, and, secondly, provided that the arterial blood is always

in tension equilibrium with the alveolar air. In normal individuals both these provisions hold true. It is undoubtedly possible to get accurate alveolar carbon dioxide tension by Haldane's method in well-trained normal subjects. So also it is entirely probable that their arterial blood is in tension equilibrium with their alveolar air, as far as carbon dioxide is concerned. In the sick patient, however, not only may it be impossible to obtain reliable Haldane samples of arterial pulmonary air, but furthermore, if there is gross pathology within the thorax it is quite possible that alveolar air and arterial blood will not be in tension equilibrium.

It was for this reason that in patients with pulmonary disease, or with those from whom for any reason we could not get good alveolar air samples, we resorted to the method of plotting the A point from the carbon dioxide content of the arterial blood. This method might at first be thought to be free from the errors of the alveolar air method, but yet, as Peters[21] has recently pointed out to us, it is not entirely so. Provided the patient made no alteration in his pulmonary ventilation while the arterial sample was being drawn, there would be no error; but supposing he, through fright or pain, either increased or decreased his ventilation, then we should have an abnormal carbon dioxide content—abnormally low in the former case, abnormally high in the latter—which would give us a false position of the A point: too far to the left in the former case, too far to the right in the latter.

Another type of possible error is due to the nature of the diagram itself. In places where the dissociation curve is more nearly horizontal than vertical, an A point plotted from the carbon dioxide tension will obviously be more accurate than that of one plotted from the carbon dioxide content; and conversely, when the curve is more nearly vertical than horizontal the carbon dioxide content will give the more accurate point. To illustrate this principle take, for example, the A point of curve No. 15. Here an increase of 1 volume per cent. in carbon dioxide content would move the A point some three times nearer the OC line than would a rise of 1 mm. in the tension; and a rise of 2.5 volumes per cent. in the content would place it on the OC line, while a rise of 2.5 mm. in tension would still leave it far to the left.

One last source of error must be mentioned, and that is the effect of oxygenation upon the level of the carbon dioxide dissociation curve. Christiansen, Douglas and Haldane[10] in their original paper showed that the curve for oxygenated blood has a definitely lower level than that of reduced blood. The curves that we have included in our normal zone were all those of oxygenated blood. Now since arterial blood is normally nearly saturated, no error is introduced in the plotting of the A point by the effect of oxygenation on the carbon dioxide capacity except with such patients as have an arterial anoxemia. It will be noted that the three pneumonia patients studied all did have arterial anoxemia. Now it might be argued that in these cases it was not legitimate for us to place an A point from the carbon dioxide content of their anoxemic arterial blood, upon a dissociation curve of fully oxygenated blood. This objection would hold except for the interesting fact just discovered by Y. Henderson that the dissociation curve of oxalated blood, that has not been exposed to air, usually shows no shift with oxygenation.[22] The shift described by Christiansen, Douglas and Haldane occurred in defibrinated blood. This finding of Y. Henderson has, we understand, been confirmed by L. J. Henderson.[23] Its explanation is yet to be discovered, but it enables us in the present research to eliminate the effect of oxygenation and reduction, and therefore to plot our A points upon a curve of fully oxygenated blood, even though they are plotted from carbon dioxide contents of anoxemic bloods.

Bearing these several considerations in mind let us now attempt the interpretation of our diagrams. We might repeat that our main object is twofold: first, to discover acidosis in the sense of diminished alkali reserve as shown by the level of the curve; and second, to discover acidosis in the sense of altered blood reaction as shown by the position of the A point, in other words, to distinguish between acidosis compensated and acidosis decompensated, and of course to discover the opposite conditions of compensated and decompensated alkalosis if such exist.

The curves obtained with the diabetic L. H. (curves Nos. 3, 4 and 5) show nothing particularly new. They illustrate very beautifully a condition of marked but compensated acidosis; that is, great reduction in available alkali but perfect pulmonary response with maintenance of normal blood reaction, and recovery therefrom.

The curves obtained with the nephritic T. C. are even more striking. When the first curve (curve No. 6) was obtained he undoubtedly was suffering from a decompensated acidosis. The change in the position of the curve over night, chiefly due no doubt to the alkali he had received, is little short of miraculous. From a condition of decompensated acidosis he had passed really in this brief interval to one of decompensated alkalosis, to use the same terminology.

The curves of the three pneumonia patients are perhaps more illuminating. Two of them, those of E. D.'s blood and of G. A.'s blood (curves Nos. 8 and 9) are within the normal zone, showing that both these patients had a normal reserve of alkali, and therefore presumably no abnormal acid in the blood; with each of them the A point is displaced in the acid direction. The curve of the third pneumonia patient, N. D., is at a higher level than normal, but like the other two its A point is displaced to the right. These A points are plotted from the carbon dioxide content of the arterial blood. As to their accuracy, we have already pointed out the effect of over- or underventilation. We have no proof that the ventilation of these patients was unaltered while we drew the arterial blood samples. However they were all very ill, and took little or no interest in the procedure. Cocainization prevented pain, and therefore there seems good reason to believe that no alteration in breathing occurred. There was no holding of the breath and no decrease in rate of breathing; that at least could be told by observation. If any change occurred then it was more likely an increase rather than a decrease. But an increase would move the A point to the left, which is the opposite to what was actually found. All things considered, then, we feel that it is reasonably certain that the hydrogen ion concentration of these pneumonia bloods was really altered in the acid direction.

In pneumonia, then, we may have in critically ill patients a condition in which, although the buffer of the blood is quite normal, the reaction is more nearly acid than normal. There is an acidosis in the latter sense, but none in the former. The only explanation of this rather paradoxical state of affairs that occurs to us is that the condition actually is one of carbonic acidosis. A person with no

non-volatile acid present in the blood, but with a pulmonary ventilation insufficient to preserve his normal $[H_2CO_3]$: $[BHCO_3]$ ratio, would have just such a diagram as these pneumonia patients. We already know because of their arterial anoxemia that they are not getting oxygen properly into their blood. It is certainly conceivable that in a similar way they are not getting carbon dioxide out. Their effective lung ventilation may be much greater than normal and still be insufficient, and it is not difficult to see how, because of mechanical limitations to the respiratory movements from pleurisy or through consolidation of the lungs, or because of decreased permeability of the alveolar membrane, the output of carbon dioxide might be hindered.

Henderson and Haggard[24] have shown that the reaction to increased carbon dioxide is an increase in the carbon dioxide capacity. This they observed in experimental morphine poisoning. It is the converse of the reaction to non-volatile acidosis. In the one case the available alkali being reduced the tension of carbon dioxide is reduced in compensation, while in the other case the tension being increased the alkali is increased in compensation. It occurred to us that this might be what was happening in the patient N. D. (curve No. 10). This curve is at a higher level than normal, yet the A point is well to the right of the OC line. The reaction of his blood then is more nearly acid than it should be, yet his available alkali is greater than normal also. This may be an attempt at compensation and it can be seen that if the carbon dioxide capacity of this blood increased only three volumes per cent. more, the A point would fall on the OC line. It very likely is only a coincidence, but it is interesting to note that this attempt at the compensation of a carbonic acidosis in this particular case proved a good prognostic sign, for this patient recovered shortly after, while the other two died.

Of the curves of the 3 cases of anemia (curves Nos. 12, 13 and 14), 2 showed a higher level than normal, that of J. B. with primary anemia being in the highest position of all the curves obtained. The curve of J. W. F. with myelogenous leukemia in an aleukemic stage and with a marked secondary anemia, was also at a higher level than normal. The A points of these two curves are also to the

left of the OC line, denoting an increased alkalinity of their blood. The curve of the other anemic patient A. W. T.'s blood is within the normal zone; the A point of this curve was not obtained.

What may be the significance of the high level of these curves in anemia we do not know. Peters[21] tells us that he has found much the same thing in some of the anemic bloods he has studied. The dissociation curve of the blood plasma lies at a higher level than does that of whole blood as shown by Hasselbalch[7] and by Joffe and Poulton[16] and it may be that the levels of anemic bloods are higher in part because of the greater proportion of plasma that they contain. For the position of the A points of these curves we also can offer no explanation. Both curves Nos. 12 and 15 are more nearly horizontal than vertical in the neighborhood of the OC line. Hence an A point plotted from tension would be more accurate than one plotted from content. That of No. 12 was plotted from tension and is, we believe, reasonably accurate. That of No. 15 was plotted from content.

The two remaining curves are that of F. M. with idiopathic tetany (curve No. 14) and of E. H. with cerebral hemorrhage (curve No. 11). The former was constructed to see whether any evidence of a condition of alkalosis could be found. None was, for the level of the curve is just above the upper limit of the normal zone and the A point on the right, not on the left, of the OC line. The curve of E. H. is, on the other hand, a little high and the A point slightly to the left. The single observation in tetany does not prove very much, for, as has been shown by Wilson, Stearns and Thurlow,[25] there are marked and rapid variations in the acid base equilibrium in tetany, and it is quite possible that our patient may have been en route from a stage of alkalosis to one of acidosis at the time the blood was drawn.

Considering the A points of the entire series, we find that they are so distributed as to indicate a range of variation in the P_h of roughly from 7.25 to 7.55. Sonne and Jarlöv,[26] calculating in a similar way, found a range of variation from 7.15 to 7.40, the difference in the P_h of our extremes thus being 0.30 and of theirs 0.25. Their highest hydrogen ion concentration was in a case of severe diabetes mellitus with acetonuria, and their lowest was in a case of chronic nephritis

with hypertension. With the gas chain Michaelis[20] has found variations from 7.74 to 7.12, the first being in a case of syphilitic hemiplegia, the second in a case of diabetic coma just before death. It seems entirely likely then that our A points are all within a range of variation compatible with life, and that they are not necessarily artefacts.

As to therapeutic indications brought out by the present study, there are one or two that are worth mention. In the first place, in regard to acidosis such as that presented by the diabetic L. H. and the nephritic T. C. While the diminution of alkali was of somewhere near the same order of magnitude, the acidosis of L. H. was apparently compensated, while that of T. C. was decompensated. It is also of interest that while L. H. had no appreciable amount of respiratory distress T. C. had a maximum amount. This we believe may in part have been due to the fact that his was a decompensated while L. H.'s was a compensated acidosis. This brings up the problem of what are the indications for alkali therapy. The curve of L. H. went back toward normal with no alkali administration in a perfectly satisfactory way, and indeed it is generally conceded now that alkali is usually unnecessary in the treatment of diabetic acidosis.

In compensated acidosis the return to a normal level is going to be accomplished by the elimination of neutralized acid by the kidney. The lungs have already done their part in preserving blood reaction. Under the circumstances it is questionable whether the giving of alkali will accomplish any great good, and indeed it is possible if too much is given that it may do harm by producing alkalosis. The indication, then, in compensated acidosis would seem to be rather to promote elimination by the kidneys by giving fluids freely, and if, as in diabetes, this is coupled with starvation, which would lessen the further production of non-volatile acid, it would seem to be sufficient therapy.

In decompensated acidosis, on the other hand, alkali administration is probably indicated, because here we have an insufficient pulmonary response. The supply of additional bicarbonate may well restore the $[H_2CO_3] : [BHCO_3]$ ratio to a normal value; indeed with T. C. it did more than that and actually pushed his reaction to

the other extreme. That it is desirable to restore blood reaction to normal cannot be doubted. The very high hydrogen ion concentrations that have been found have all been in critically ill patients, who usually in fact were in a moribund state. On the other hand, it is undoubtedly quite as important not to overdo the alkali therapy, as was done with our patient T. C. A warning that excessive alkali therapy may be harmful has been given by Allen, Stillman and Fitz.[27] They believe, particularly in persons with damaged kidneys, that alkali should be used with great caution. That tetany can be produced after alkali administration is in itself evidence that alkalosis as well as acidosis may be harmful *per se* and equally to be avoided. The case reported by Harrop[28], of a woman with mercuric chloride poisoning who developed tetany and showed a plasma bicarbonate capacity of 80 volumes per cent. after the intravenous injection of 60 grams of sodium bicarbonate, is particularly interesting in this regard. Equally pertinent is the recent work of Grant and Goldman,[29] who succeeded in producing tetany and other unpleasant symptoms in themselves by prolonged voluntary forced breathing. They were able at the same time to demonstrate a change in the P_h of the blood in the alkaline direction, and had the interesting situation of a low position of the dissociation curve as shown by the alveolar carbon dioxide tension and the carbon dioxide capacity of the plasma and at the same time a blood more alkaline in reaction than normal. It really is the diametrically opposite condition to that shown by our pneumonia patient N. D. (curve No. 10).

As to the indications for treatment in pneumonia, we can only say that they would seem to be to facilitate lung ventilation. According to our present knowledge, however, such indications can only be indirectly met. Measures which facilitate the mechanics of respiration, the relief of pleural pain, the placing of the patient in the upright position, are of this order. So too are specific or other forms of treatment which by reducing fever decrease the metabolism, and hence the carbon dioxide output, and so decrease the amount of ventilation necessary to preserve the normal acid-base ratio. As Hoover[30] has pointed out, anoxemia may or may not be relieved by oxygen administration, but in any event difficulties in

carbon dioxide elimination cannot be so relieved, and consequently it seems unlikely that oxygen administration will have any great beneficial effect in the treatment of pneumonia. Several years ago Newburgh, Means and Porter[31] showed that the respiratory center gradually fails during the course of experimental pneumonia. It has also been shown by Davies, Haldane and Priestley[32] that resistance to breathing actually causes fatigue of the center. It is quite possible that the failure of the center noted by Newburgh, Means and Porter was in part due to such fatigue, the fatigue resulting from an incompletely successful respiratory effort to overcome a tendency toward carbonic acidosis.

V. SUMMARY. "Carbon Dioxide Diagrams" (Haggard and Henderson) have been constructed for the bloods of a series of hospital patients as a method of studying disturbances in their acid-base equilibrium.

A diabetic with a low level of blood alkali, but with a normal blood reaction, a compensated acidosis in other words, showed a rapid return toward normal with no treatment but starvation and increased water and salt intake.

A nephritic with a decompensatec acidosis and a very low blood alkali was rapidly brought to a condition of decompensated alkalosis with a high blood alkali by the therapeutic administration of sodium bicarbonate.

It is suggested that the therapeutic use of alkali in acidosis is probably only indicated in the decompensated variety, and that there it should be controlled carefully and that the production of alkalosis should be avoided.

The diagram obtained in three pneumonia patients suggested that they were suffering from a condition of carbonic acidosis, due perhaps to insufficient pulmonary ventilation.

In 2 out of 3 cases of anemia, the dissociation curve was found to lie at a higher level than normal. No explanation for this finding was offered.

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DISCUSSION

Dr. C. F. Hoover, of Cleveland, Ohio, asked if Dr. Bock found his results inconsistent with the anoxemia of pneumonia, due to the contribution of unexpired blood to the aortic stream. In these patients, giving them pure oxygen would not move the cyanosis. There is an interstitial edema, just as in edema of the lungs with multiple thrombi. The cyanosis from alveolar edema could not be moved, and the CO_2 could not be modified at all; but in a man with phosgene poisoning, giving oxygen would modify the cyanosis. The phosgene patient could not tell whether he was breathing oxygen or not.

Dr. Bock said he could not explain the anoxemia. He thought that what Dr. Hoover said was correct. CO_2 was apparently accumulating. They had made determination to find out what oxygen was present. An accumulation of CO_2 would show that the ventilation was insufficient.

Dr. Hoover said that recently Haldane had made the statement that anoxemia was due to the rapid breathing, but one also found anoxemia with slow breathing.

Dr. Bock said that the patients did not seem to expire the CO_2. They could not get rid of it.

Dr. Hoover said they did in a measure compensate for the CO_2 but not for the anoxemia.

Dr. Bock said these patients could not accomplish ventilation enough to preserve the ratio.

THE PRODUCTION OF GENERALIZED SYPHILIS IN THE RABBIT BY LOCAL INOCULATION

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For many years, students of syphilis have been seeking means of producing an experimental infection in laboratory animals which would meet the needs for the investigation of problems of human syphilis. The earlier attempts to transmit the disease to animals were unsuccessful but in 1904 it was shown that an infection comparable to that in man could be produced in the higher apes and a less characteristic condition was obtained in certain species of monkeys. The usefulness of these infections was necessarily rather restricted on account of the animals employed and attention was directed to the development of some other type of experimental object.

The rabbit seemed to offer the most hopeful solution of this problem and eventually it was shown that a widespread infection could be produced in a considerable proportion of animals by intracardial or intravenous injection of massive doses of Treponema pallidum. Of course, this type of infection did not reproduce the sequence of events as they occur in man and while the lesions were no more than multiple primary lesions, the experiments served to show a general suceptibility of the rabbit's tissues to pallidum infection.

Simple, local inoculation failed to give the desired result but brought out an interesting paradox in the animal reaction. It was found that the rabbit could be readily infected and reacted with

the formation of a lesion at the site of inoculation which was closely analogous to that in man; in some instances at least, the organisms became widely distributed through the body of the infected animal and yet the occurrence of lesions other than those at the site of inoculation was extremely rare. In contrast to the infection which occurs in man, the striking features of that produced by local inoculation in the rabbit were the marked reaction at the site of inoculation and the total absence of other lesions.

Various explanations might be offered for this apparently anomalous condition but from the facts at our disposal, it appeared that the underlying cause for the absence of generalized lesions in the rabbit was to be found in the reaction at the site of inoculation. Thus, out of 126 rabbits in our series which had shown generalized lesions,[1] the majority of them belonged to one of three categories:

1. Animals in which the initial reaction had been slight.

2. Animals which had been subjected to operative removal of primary lesions.

3. Animals whose primary lesions had been reduced by the administration of some therapeutic agent.

An analysis of the cases of generalized syphilis reported in the literature also showed that a surprisingly large proportion of those observed by other investigators belonged either in Class 2 or were animals which had been inoculated at one instead of several foci as has been a common practice.

From these facts, we were led to believe that under ordinary circumstances the marked reaction which followed a bilateral inoculation in the testicles or scrotum of the rabbit might be sufficient in itself to exercise a considerable influence over all other manifestations of disease and to inhibit the development of generalized lesions. In like manner, it appeared that any condition or influence which tended to reduce or to suppress this reaction might remove or diminish its inhibitory effect and thus favor the development of other lesions.

This hypothesis was subjected to experimental test but before

[1] For a description of the manifestation of generalized syphilis in the rabbit, the reader is referred to a series of papers by the authors in the Journal of Experimental Medicine, 1920, xxi, beginning with page 709.

undertaking the experiments which we had in mind, it was considered necessary to determine the facts as to the frequency and extent of the dissemination of the infecting organisms following a local inoculation.

Dissemination of Spirochetes from the Point of Inoculation. The spread of organisms from the point of inoculation was studied by a systematic examination of the inguinal lymph nodes of rabbits inoculated in the scrotum and by examination of blood drawn from the hearts of animals inoculated either in the scrotum or testicles.

Lymph Nodes. The procedure adopted for determining the presence of spirochetes in the lymph nodes was to remove the node with aseptic precautions under ether anesthesia; the node was then minced and ground in a sterile mortar and an emulsion prepared by the addition of about 1.5 c.c. of sterile salt solution. The emulsion thus prepared was injected into one testicle of two normal rabbits and the presence of spirochetes determined by the development of an orchitis within sixty days after inoculation.

Nodes from 27 rabbits were examined by this method at intervals of from forty-eight hours to sixty-one days after inoculation. All of them proved to be infective with a comparatively short period of incubation. In 2 other cases, spirochetes were demonstrated in material from the nodes by dark field examination and no inoculations were made. It was thus shown that virulent spirochetes gained access to the regional lymphatics at a very early period of the infection—in fact before any lesion at the site of inoculation could be recognized.

Heart's Blood. The second set of experiments on the dissemination of spirochetes was carried out by drawing 5 to 10 c.c. of blood from the heart of an infected animal and defibrinating; 0.5 c.c. of this blood was then injected into each testicle of two normal rabbits and the results of the experiment determined as in the preceding case.

A total of 81 bleedings was made on a series of 37 rabbits at intervals of from seven to ninety-nine days after inoculation. Without giving the detailed results of these experiments, it is sufficient to say that spirochetes were demonstrated in the blood of all the animals, indicating that invasion of the blood stream always

occurred after a local inoculation and again that this might take place even before the development of a primary lesion.

Influence of the Reaction at the Site of Inoculation upon the Development of Generalized Lesions. When it had been determined that early and widespread dissemination of spirochetes always occurred following a local inoculation, we were prepared to test our hypothesis as to the influence which the reaction at the site of inoculation might exercise upon the occurrence of generalized lesions. This was done in four ways: (1) By comparing the results obtained from the inoculation of one and of both testicles; (2) by determining the effects of unilateral and of bilateral castration at an early period of the infection; (3) the effects of suppression of the local reaction by the use of a therapeutic agent administered in doses capable of inducing resolution of the lesions but not sufficient to destroy the infecting organisms; and (4) by complete prevention of a primary reaction. This was accomplished by extirpation of the entire area surrounding the site of inoculation at the end of forty-eight hours. All operative procedures were carried out under ether anesthesia.

Unilateral and Bilateral Inoculations and Effects of Castration. In the first series of experiments, there were 27 rabbits inoculated in one testicle and 20 inoculated in both testicles. These animals were divided into two groups one of which was castrated soon after the appearance of the testicular lesion and the other held as controls. The results of the experiments were determined upon the basis of four months' observation.

The effect of inoculating one as compared with both testicles may be indicated by the results obtained from the uncastrated controls of the two series.

	Number of animals.	Generalized lesions.
Bilateral inoculation	6	1
Unilateral inoculation	13	8

It was apparent that this one procedure of reducing the primary lesions by one-half had a very decided influence upon the development of other lesions and this effect was still further augmented when the infected organs were moved.

	Number of animals.	Generalized lesions.
Bilateral inoculation and castration	14	13
Unilateral inoculation and castration	14	13

These effects were still further checked by a comparison of the effects of unilateral and bilateral castration of animals inoculated in both testicles. This experiment gave the following results:

	Number of animals.	Generalized lesions.
Bilateral castration	5	5
Unilateral castration	5	1

The removal of one of the two foci of primary reaction in this case was sufficient to permit the development of lesions other than those in the testicles in only 1 out of 5 cases. This procedure was not as effective as if the animal had originally been inoculated in only one testicle. Whether this would prove to be true in a larger series of animals cannot be said.

Suppression of Primary Lesions by the Use of a Therapeutic Agent. The series of animals in which the effects of suppression of the primary lesions by the use of a therapeutic agent was tested, consisted of 46 rabbits, one-half of which was inoculated in one testicle and the other in both testicles. The drug used in these experiments was arsenophenylglycyl dichloro-m-aminophenol which had been studied by us in collaboration with Dr. W. A. Jacobs and Dr. Michael Heidelberger and found to possess a relatively greater effect upon syphilitic lesions than upon the spirochetes.

Six rabbits from each of the two series were given a single intravenous injection of 5.0 mg. of this drug, per kilo, fourteen days after inoculation. The results of the drug administration were controlled in two ways: By the use of an equal number of untreated animals from each series and by castrations performed upon the remaining animals at various periods of observation. All of these animals were observed for a period of three months after inoculation.

The results of castration need not be given further than to say that they conformed to those previously reported. The effect of the drug upon the testicular lesions of the animals inoculated in one testicle was to induce almost complete resolution and to suppress further reaction in the testicle for between two and three weeks. The effect was less marked in those inoculated bilaterally and lasted for only about seven to ten days. The end-result of the experi-

ment as regards the development of generalized lesions may be summarized as follows:

	Number of animals.	Generalized lesions.
Bilateral series:		
Untreated controls	6	1
Treated animals	6	5
Unilateral series:		
Untreated controls	6	3
Treated animals	6	6

It was thus shown that suppression of the primary lesions in the testicle by the use of a therapeutic agent might have an influence upon the development of generalized lesions fully as marked as that of a reduction of the reaction, either by the type of inoculation employed or by excision of the lesions and that there was an apparent relationship between the extent of the suppression and the subsequent occurrence of generalized lesions.

Complete Prevention of a Primary Reaction. A final experiment giving the effects of complete prevention of a primary reaction still further illustrates this feature of the relation between the reaction at the site of inoculation and the occurrence of generalized lesions. In this experiment, 10 rabbits were inoculated in the right scrotum only by inserting a small bit of infected tissue beneath the skin of the scrotum. At the end of forty-eight hours, the scrotum and testicle of that side, together with a wide zone of skin, were excised under ether anesthesia. Following operation, the wounds healed and no syphilitic lesions developed in this region.

By the end of the seventh week, 8 of the 10 rabbits had developed marked generalized syphilis and slight lesions appeared in the other 2 animals at two and two and a half months after inoculation. On the whole, the infection thus produced was the most pronounced which we have seen in any single group of animals.

Conclusions. These experiments would appear to establish the existence of an interrelation between the reaction which takes place at the site of inoculation in the rabbit and the subsequent occurrences of other manifestations of disease. They indicate that the reaction about the primary focus of infection may exercise an inhibitory influence upon the development of other lesions; that this influence bears a measurable relation to the intensity

and the extent of the primary reaction and that it may be so great as to completely prevent the development of generalized lesions.

It is further shown that this influence is itself susceptible to experimental variation—that it may be augmented, diminished, or suppressed and that the incidence and severity of generalized lesions will vary accordingly.

In view of these facts, it appears that intensive and multiple inoculations, as generally practised in the rabbit, together with the inherent tendency on the part of the animal to exhibit a marked primary reaction to infection with Treponema pallidum have contributed largely to the low incidence of generalized lesions following local inoculation; that by the use of simple procedures which obviate these difficulties, a generalized disease may be produced which presents many of the characteristics of human syphilis.

DISCUSSION

Dr. Homer F. Swift, of New York, said that this was a very interesting and important contribution. This experimental work had a bearing on the treatment of human syphilis. It had been noted in the army work that when the drug was used to cure the lesion but not to kill the spirochetes, the reactions were more severe than if the syphilis had been allowed to run its course. This was the first time such a conclusion had been demonstrated in a convincing manner. A note of warning should be sounded: this demonstration of the generalization of the spirochete so early might have something to do with letting down the use of prophylactic measures after exposure. Local prophylaxis was effective for a certain number of hours. This type of inoculation was different from that which occurred in human syphilis. This work might explain the mode of transmission of the virus into the deeper organs.

Dr. George Blumer, New Haven, said that there had been periods when attempts had been made to prevent syphilis by excision of the primary sore. In Dr. Brown's work the excision of the chancre led to unusually rapid dissemination of the disease.

Dr. Wade H. Brown (closing) said that the status of the disease in the human being as regards magnitude of the primary lesion and the generalized reaction was different, but generalization could occur in the human being as early as in the rabbit. If the cases were not treated following excision,

they got a more pronounced reaction. That, however, did not contra-indicate excision of the chancre. In rabbits the local lesion had a necrotic center in which the spirochetes might survive. In cases well treated there was a chancre redux, but in human cases he did not think that excision of the chancre would prevent generalization. The organism in experimental work could be recovered from the lymph nodes and from the general circulation long before they could excise the chancre. In regard to treatment of early cases, although generalization might have taken place, lesions had not developed. The symptoms had to be treated, on account of the pathological nature of the object one was trying to overcome.

AN ACUTE RESPIRATORY DISEASE IN MAN FOLLOWING INOCULATION WITH A VIRULENT BACILLUS INFLUENZÆ

By RUSSELL L. CECIL, M.D.
AND
GUSTAV I. STEFFEN

The two epidemics of influenza which have swept over the country since the fall of 1918 have served to concentrate the attention of bacteriologists once more on the etiology of this disease, and a considerable amount of their interest has been centered on the part played by the influenza bacillus. During the last two years a number of investigators have tried to produce influenza in man by direct inoculation of Bacillus influenzæ cultures into the healthy nose and throat. Almost without exception, however, these efforts have resulted in failure.

Blake and Cecil,[7] in a recently published article, have shown that by inoculating monkeys in the nose and throat with a virulent culture of Bacillus influenzæ, an acute infection of the upper respiratory tract may be induced which is clinically similar to influenza in man. In these experiments, the strain of influenza bacillus employed was first rendered virulent for the species by repeated intraperitoneal injections. By this procedure, the culture eventually became so virulent for monkeys that the inoculation in the nose and throat of only a small quantity of either the peritoneal exudate or a blood broth culture would initiate in a few hours an acute respiratory infection characterized by sneezing, coughing, mucopurulent discharge, leukopenia, prostration and fever. Furthermore, several of the monkeys thus infected devel-

oped later a hemorrhagic bronchopneumonia from which Bacillus influenzæ was recovered at autopsy.

If monkeys could be infected so readily with a virulent strain of B. influenzæ, it seemed reasonable to suppose that, by use of proper methods, a similar experimental disease could be produced in man. The experiments reported in this paper were undertaken with such an object in view.

METHODS. 1. *Culture Media.* The culture media consisted of freshly prepared "chocolate blood" agar and broth, and the sodium oleate hemoglobin agar of Avery. The chocolate medium was prepared by adding defribinated horse or rabbit blood to veal infusion agar or broth, and the mixture heated at 70° C. for a few moments until the blood changed color. The titration of the medium was Ph 7.4 to 7.6.

2. *Cultures.* Two strains of Bacillus influenzæ were employed in these experiments. Both were isolated in almost pure culture from typical cases of influenza admitted to the Willard Parker Hospital during the epidemic of February, 1920. These two strains presented all the morphological and cultural characteristics of the Pfeiffer bacillus and failed to grow on blood-free media.

Strain "Graham" was cultivated from the throat of a child with influenza and influenzal pneumonia. This strain was used in only one experiment. As the results were negative, it was discarded and another culture (strain "Wick") was substituted for the remaining experiments.

Strain "Wick" was isolated by Dr. A. W. Williams in conjunction with Streptococcus hemolyticus from the pleural exudate of a young woman who died of influenzal pneumonia and empyema. This strain was found to be virulent for both rabbits and mice. A rabbit injected intraperitoneally with 2 c.c. of a young chocolate blood broth culture died in five hours, and 0.25 c.c. of an eighteen-hour culture of the same strain killed a mouse in less than twenty-four hours.

3. *Volunteers.* The volunteers selected for these experiments were healthy adults, either medical students or laboratory workers. Of the six individuals inoculated with Bacillus influenzæ, three gave a history of influenza during the epidemic of 1918–19. The

other three denied having had the disease. Preliminary cultures were taken in every case from the nose and throat to eliminate influenza bacillus carriers. One carrier, however, was purposely inoculated in order to determine whether the presence of influenza bacilli in the nose and throat conferred any immunity against experimental infection. No volunteers were accepted who gave a history of any recent respiratory infection.

In addition to the six volunteers inoculated with influenza bacilli, six other volunteers were selected for control inoculations. Two of these received the filtrate from a chocolate blood broth culture of Bacillus influenzæ; two were inoculated with a virulent Streptococcus hemolyticus and the remaining two were tested with a virulent pneumococcus of No. IV group.

All the volunteers were kept under close observation during the period of the experiment. Temperature, leukocyte counts and cultures were frequently taken, and the subjects were carefully examined twice a day for any local or general reaction.

When the influenza bacillus was recovered from cultures taken on the volunteers subsequent to inoculation, the strain was studied by means of agglutination and absorption tests to establish its identity with the strain inoculated. These tests were carried out by Dr. Olga R. Povitzsky, of the Research Laboratory of the N. Y. City Department of Health, in connection with a biological study of influenza bacilli undertaken by her simultaneously with the experiments herewith reported.

Inoculation of Volunteers with Washings from Chocolate Blood Agar Slants of Bacillus Influenzæ. Two healthy volunteers were inoculated in the nose and throat with freshly isolated strains of Bacillus influenzæ, which had been cultivated for eighteen hours on chocolate blood gar slants. The growth was washed from each slant with 1 c.c. of sterile broth, and made a fairly thick suspension. One of these volunteers gave a history of influenza during the epidemic of 1918; the other denied having ever had the disease. Preliminary cultures showed that neither of these volunteers carried influenza bacilli.

In the first case one-half slant of influenza bacillus culture produced practically no local symptoms whatever. There was slight

malaise for several days following the inoculation and a frontal headache which lasted only twenty-four hours. Influenza bacilli disappeared from the nose and throat in a remarkably short time. Cultures taken six hours after inoculation were entirely free from influenza bacilli. There was no rise in temperature at any time, and that the leukocyte count remained practically unchanged.

The second volunteer received an entire chocolate blood agar slant of Bacillus influenzæ culture in each nostril, and a different strain (strain "Wick") was employed for the inoculation.

This volunteer appears to have been definitely infected by the inoculation. Both the local and constitutional symptoms were marked, and influenza bacilli were present in smears from the nostrils twenty-four hours after the injection of the culture. The temperature and leukocyte curves showed nothing of interest. The most striking features in this case were the headache and general malaise, and the well marked local inflammation in the nose and throat.

From these two experiments it would appear that an acute respiratory infection can be produced by the inoculation of chocolate blood agar slant cultures of Bacillus influenzæ, if a sufficiently large dose of culture is employed.

Inoculation of Volunteers with the Peritoneal Exudate from a Monkey with Bacillus Influenzæ Peritonitis. Blake and Cecil[7] were quite successful in producing experimental influenza in monkeys by direct inoculation with the peritoneal exudate from a monkey with Bacillus influenzæ peritonitis. It seemed desirable, therefore, to try this method of experimental infection on human volunteers. The exudate was obtained by inoculating a Rhesus monkey intraperitoneally with a large amount (20 plates) of influenza bacillus culture. Twenty-four hours later the monkey was dead. The cloudy exudate, containing large numbers of influenza bacilli in pure culture, was removed from the peritoneal cavity with a sterile pipette and was injected immediately into the nostrils of the volunteers.

Two volunteers were inoculated with peritoneal exudate. The dose in both cases was quite small, only 0.1 c.c. of exudate in each nostril. In addition, the throats of the volunteers were rubbed with a cotton swab which had been soaked in the exudate.

The first case was particularly interesting on account of the relapse which he experienced one week following the inoculation. The mild infection which developed immediately after the inoculation of Bacillus influenzæ had about run its course when, following exposure to cold, the patient developed a much more severe respiratory infection which involved the nose and throat and trachea and which necessitated his going to bed. Strangely enough, agglutination and absorption tests carried out with the cultures of Bacillus influenzæ isolated during the relapse indicated that this strain was entirely distinct biologically from the strain which was originally inoculated, and which had been isolated from the nose and throat during the first mild infection. The temperature and leukocyte curves in this case showed practically no deviation from the normal. There was a very slight elevation of temperature at the onset of the relapse but this was only temporary.

The second volunteer received the same dose of peritoneal exudate that the first volunteer received. In spite of the small quantity of fluid injected (0.1 c.c. in each nostril) he promptly developed a characteristic chain of symptoms.

In addition to coryza and cough, prostration was quite marked and the headache and pains in the extremities were also characteristic. The leukocyte curve in this patient showed a definite leukopenia, the count going down from 9300 to 6000. The temperature, as in the previous cases, remained normal. In fact, it was subnormal on the day following the inoculation. It is interesting to note that in this case influenza bacilli were still present in large numbers in the patient's throat four weeks after the inoculation.

Inoculation of Volunteers with Young Chocolate Blood Broth Cultures of Bacillus Influenzæ. Two volunteers were inoculated with a six-hour chocolate blood broth culture of Bacillus influenzæ. The strain used for these inoculations was the same one used in the previous experiments with peritoneal exudate, but in this instance freshly isolated from the throat of Case IV. As in the two previous cases, very small quantities of culture were inoculated. These two volunteers each received 0.5 c.c. of culture in either nostrils but as the culture was very young the actual number

of bacteria injected was comparatively small. We were prompted to use the young cultures by the work of Parker,[8] who found that six-hour cultures of Bacillus influenzæ were more toxic than older cultures.

The first volunteer reacted to inoculation in a manner quite similar to that of the two preceding cases. The temperature was not elevated at any time; twelve hours after inoculation the temperature was actually subnormal (95.6°). This patient showed a very striking leukopenia, the leukocytes falling from 12,000 to 6000. This patient became an influenza bacillus carrier following his attack of experimental influenza. Cultures from the throat were positive for influenza bacilli for two or more months following inoculation.

The second volunteer differed from all the preceding cases in that he was a carrier of the influenza bacillus at the time of inoculation. It seemed desirable to inoculate one carrier purposely in order to determine whether the carrier state conferred any immunity against infection by this organism. The method of inoculation was similar to that employed in the preceding case.

This patient ran a somewhat milder course than the other volunteers and the question naturally arises whether the mildness of his attack was dependent in any way on the fact that he was already an influenza bacillus carrier. Agglutination and absorption tests indicated very clearly that the strain which he carried and the strain which was inoculated were entirely distinct biologically. It is possible, however, that there was some cross-protection conferred by the strain which the volunteer carried. Here as in the previous cases the temperature remained stationary and the leukocytes dropped; indeed, the temperature also dropped following the inoculation and went down as low as 96.5° F. The leukocyte curve was quite similar to that observed in Case V. The patient's count before inoculation was 11,500. Following inoculation it gradually went down until it reached 6500 on the second day of his infection. This experiment would appear to indicate, however, that influenza bacillus carriers are not necessarily immune to infection by the influenza bacillus. Such a conclusion is in agreement with observations on carriers of other pathogenic bacteria.

Inoculation of Volunteers with Filtration of Bacillus Influenzæ Cultures. In order to determine whether the symptoms produced by inoculation with Bacillus influenzæ were due to a genuine infection or merely to the absorption of a toxic substance, two volunteers were inoculated with a filtrate from a young chocolate blood broth culture of Bacillus influenzæ. After six hours' incubation the cultures were passed through a Berkefeld filter, and the filtrate inoculated at once into the volunteers. The same strain (strain "Wick") that was used for the preceding experiments was employed for the filtrate inoculations, and each volunteer received 0.5 c.c. of filtrate in either nostril.

Neither volunteer developed any symptoms following the inoculation. From these two experiments it would appear that filtrates of young cultures of Bacillus influenzæ are incapable of producing acute inflammatory symptoms in the nose and throat of healthy volunteers. It has been shown by Parker[8] that young cultures of Bacillus influenzæ contain a toxic substance, small doses of which will kill rabbits in a few hours. There was a possibility, therefore, that the symptoms produced by the intranasal injection of Bacillus influenzæ cultures were referable to absorption of this toxin. The negative results, however, obtained with filtrates from the cultures eliminate such a possibility.

Inoculation of Volunteers with Young Blood Broth Cultures of Streptococcus Hemolyticus. It seemed desirable to control the experiments with Bacillus influenzæ still further by inoculating some volunteers with other pathogenic bacteria. Accordingly, two volunteers who did not harbor Streptococcus hemolyticus in their noses or throats were selected for inoculation with a strain of Streptococcus hemolyticus freshly isolated from the tonsils of a young woman with acute follicular tonsillitis and peritonsillar abscess. This organism was fairly virulent, 0.1 c.c. of a blood broth culture killing a mouse in twenty-four hours. Each volunteer received 0.5 c.c. of chocolate blood broth culture in either nostril.

In the case of the first volunteer the inoculation of a virulent Streptococcus hemolyticus gave practically negative results. The temperature and leukocytes remained normal. The patient had

no constitutional symptoms whatever, and locally the only change noticed was a slight dryness in the throat which lasted only a few hours. In spite of the failure, however, of the hemolytic streptococcus to produce infection in the volunteer the organism remained in the patient's throat for a week, and perhaps longer, following the inoculation.

The second volunteer in this experiment received the same strain of Streptococcus hemolyticus and the same amount of culture as Case IX received. The results, however, were more definite.

The volunteer developed an acute follicular tonsillitis following the inoculation. The infection, however, was a mild one and lasted only three days. There was a moderate febrile and leukocyte reaction, and mucopurulent exudate over the tonsils. The patient was practically free from malaise. Headache was present, but not severe. Hemolytic streptococci persisted for five days, and perhaps longer, in the nasopharynx.

Summarizing these two experiments with the Streptococcus hemolyticus, it may be said that the inoculation of healthy volunteers with a virulent Streptococcus hemolyticus produces either no symptoms at all or gives rise to an acute tonsillitis with fever and leukocytosis.

Inoculation of Volunteers with a Young Blood Broth Culture of Pneumococcus. As a further control on the Bacillus influenzæ inoculations two volunteers were selected for inoculation with a virulent pneumococcus. For this experiment two healthy young men were chosen whose preliminary cultures showed them to be free from pneumococci. A freshly isolated, highly virulent pneumococcus, Type IV was used for these inoculations. This strain had been obtained from the sputum of a child with influenzal pneumonia. Each volunteer received 0.5 c.c. of a six-hour chocolate blood broth culture.

The first volunteer showed no reaction, either local or general, to inoculation with a pneumococcus Type IV, though the culture inoculated was highly virulent for mice and had been freshly isolated from a case of influenzal pneumonia.

A second volunteer was inoculated with the same culture of pneumococcus and he too failed to develop any symptoms.

The negative results obtained in these two volunteers indicate that in man the inoculation of virulent pneumococci in the healthy nose and throat is not sufficient to induce a pneumococcus infection of the upper respiratory tract.

Discussion. The results obtained in these experiments confirm in almost every particular, the studies on experimental influenza recently carried out by Blake and Cecil on monkeys. In both instances, the inoculation of virulent influenza bacilli has given rise to an acute respiratory disease, very similar to clinical influenza, and characterized by the presence of influenza bacilli in the discharges. In monkeys the hemolytic streptococcus, when inoculated in the nose and throat caused no reaction. In man, however, one of the two volunteers developed an acute tonsillitis from which the Streptococcus hemolyticus was recovered. In both species virulent pneumococci failed to excite symptoms.

In view of the failure of most previous experimenters to produce a respiratory infection in man with the influenza bacillus, it is interesting to speculate as to the reason for success in our own experiments. The use of freshly isolated, virulent strains was probably an important factor. The character of the culture medium employed also appeared to have considerable influence. The first experiment with the washings from chocolate blood agar slants was practically negative. The second experiment with the same sort of suspension was fairly successful, but a large dose (one slant in each nostril) was employed, and the symptoms produced were quite temporary. The two experiments with small doses of peritoneal exudate from a monkey with Bacillus influenzæ peritonitis were quite successful, and so were the last two experiments with small doses of young chocolate broth culture. It would appear, therefore, that fluid cultures were more likely to produce positive results than the washings from solid media.

As to the character of the infection produced by these inoculations, the most that can be said is that the experimental disease closely simulated the milder forms of spontaneous influenza. The short period of incubation in the experimental disease agrees entirely with clinical observations as to the incubation period of genuine

influenza. In respect to the local manifestations the analogy is complete. The onset with sneezing, rhinitis and sore-throat, followed in some cases by tracheitis, presents a faithful reproduction of influenza. The systemic reaction in the experimental disease was not so profound as in true influenza, and resembled more the prostration which accompanies a severe cold or bronchitis. It may be remarked in passing, however, that many common colds are apparently due to the influenza bacillus. Headache was noted in 5 of the volunteers. The prostration in Case 3 was quite marked, and Cases 4 and 5 were in bed during part of their illness. Leukopenia was present in 3 of the cases (Nos. 4, 5 and 6); in the other 3, the leukocytes remained practically unchanged. Here again the findings were in harmony with clinical influenza, and with the experimental infections produced in monkeys. The absence of fever in all 6 cases was rather surprising and constituted a point of divergence from typical influenzal infections, as seen in the epidemics. The occurrence of severe influenza without a rise of temperature is not unusual, however. The fatal case of influenzal pneumonia from which strain "Wick" was isolated and with which 5 of the volunteers were inoculated had been in the hospital only forty-eight hours when death occurred. During that time, however, the temperature never rose above 99° F.

The influenza bacillus was recovered from the nose and throat of the 5 volunteers that developed local symptoms. In one case the influenza bacilli had disappeared twenty-four hours after inoculation. In the 4 remaining cases (those that received Bacillus influenzæ exudate or blood broth culture) influenza bacilli persisted in the nose or throat for several days or even weeks after inoculation. Many of the plate cultures taken at the height of the infection gave almost pure growths of Bacillus influenzæ.

The experiments with filtrates of Bacillus influenzæ cultures clearly eliminate the possibility that the results obtained in these experiments might have been referable to some soluble toxic substance. Even admitting that a small portion of the toxin remained behind in the filter, this must have been a very inconsiderable part of the whole, and not enough to have materially affected the result. There is abundant clinical and bacterial evidence that we were dealing in these cases with genuine infections.

The experiments with the hemolytic streptococcus are interesting and corroborate the findings of Richey[9] who noted a number of cases of Streptococcus hemolyticus tonsillitis following inoculation of healthy volunteers with the washings from the noses and throats of cases of influenza. It is probable that altogether aside from the question of virulence, the results following inoculation with Streptococcus hemolyticus depend largely on the source of the strain. In this particular instance, a strain isolated from a case of acute tonsillitis with peritonsillar abscess, excited an attack of acute tonsillitis in one of the volunteers inoculated with the culture.

A virulent pneumococcus Type IV, isolated from a case of influenzal pneumonia, was inoculated in the nose and throat of two volunteers and failed to excite any symptoms whatever. It should not be inferred from these two experiments, however, that the pneumococcus never acts as the primary infectious agent in acute infections of the nose and throat. It is possible that pneumococcus and certain others of the bacteria that are associated with coryzas and sore-throats invade the tissue only after some local or general depression in the resistance of the host. The recently published experiments of Grant, Mudd and Goldman[10] bear out this theory. The capacity of all these bacteria to act as secondary invaders cannot be questioned; but the experiments reported in this paper indicate that virulent influenza bacilli possess a peculiar power of attacking healthy mucous membrane and of exciting a respiratory infection quite similar in its clinical manifestations to spontaneous influenza.

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DISCUSSION

Dr. George Kober, of Washington, said that he thought it might be of value to recall facts as to the epidemic constitution of the atmosphere. This was evident in malaria and scarlet fever. In agriculture there was a great difference in the quality and quantity of crops of vegetables and fruits which was attributable to meteorological influence. Why should not a similar influence have an effect on unicellular organism?

Dr. Bunting, Madison, Wis., said that in 1920, during the epidemic in Madison, they made daily blood counts, in order to throw light on the leukocytic findings. There was an almost immediate leukopenia and inhibition of the marrow cells in uncomplicated cases. In the lung cases there was an immediate leukocytosis and that occurred before the clinician could tell what had developed. It was coincident with the first clouding of the lung, as observed by the *x*-ray, so that it seemed that there was inhibition of the marrow, as in typhoid fever, if the leukopenia was due to pyogenic cocci. The Pfeiffer bacillus was found to produce profound bone marrow changes in rabbits. The evidence was rather in favor of the Pfeiffer bacillus than a coccus, because of the bone-marrow picture.

Dr. Joseph H. Miller, Chicago, said that there was leukopenia in a streptococcus epidemic, associated with measles, and frequently leukopenia in a streptococcus pneumonia.

Dr. E. C. Rosenow, Rochester, Minn., said that Dr. Kober's point was interesting. Evidently contact played an important part in the epidemic, but the reason was not known. There was an increase and decrease of virulence of organisms associated with season. The type of reaction in the animal might change completely, though the microbe was the same throughout. It might not be true that pneumonia occurred with the advent of a secondary invader, because of the prolongation of resistance might change the organism, so that, instead of leukopenia, a leukocytosis might be produced.

THE BREATHING OF AIR OF LOWERED OXYGEN TENSION AS A TEST OF CIRCULATORY FUNCTION

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(ABSTRACT)

Henderson and his co-workers[1] [2] have recently reported favorably on the value of gradual lowering of oxygen tension of respired air by means of a rebreathing apparatus as a test of cardiac function. While these workers speak of the test as one of cardiac function, it is apparent that the work of the heart alone, in the adaptation to anoxemia, cannot be separated from that of the circulatory function as a whole.

The response to anoxemia involves a number of body mechanisms, the relative importance of which has not been definitely settled. Gregg, Lutz and Schneider[3] state that individuals differ in their responses to low oxygen tension, pointing out that some compensate largely by increased respiration, while others depend almost wholly on increased blood-flow. Haldane, Kellas and Kennaway,[4] on the other hand, held that anoxemia cannot be compensated for by mere increase in breathing or circulation; the advantage gained by higher

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[4] Haldane, J. S., Kellas, A. M., and Kennaway, E. L.: Jour. Physiol., 1919, liii, 181.

saturation of the blood with oxygen in the lungs is counteracted by the increased sweeping out of carbon dioxide resulting in shifting of the dissociation curve for oxyhemoglobin. Owing to this, the hemoglobin combines more readily with oxygen in the lungs but holds on to it more tightly in the tissues, so that the supply is not much improved, although the blood is redder.

We have attempted to determine the usefulness of the rebreathing apparatus for clinical purposes in hospital work, especially with respect to its value in estimating circulatory efficiency. We have selected for presentation from our material the result of studies in five cases of heart disease and two of pneumokoniosis. All the cardiac cases were on the verge of decompensation, or slightly decompensated. All had hemoglobin percentages of 75 or more (Sahli). None showed any arrhythmia nor developed any during the test except occasional slight sinus arrhythmia coincident with increased breathing. The cases of pneumokoniosis were fairly well advanced in the so-called second stage. They were studied in the effort to learn to what extent pulmonary lesions of their type might be expected to interfere with the aëration of the blood while breathing air with lowered oxygen content.

Methods. A rebreathing apparatus was used similar to the one described by Henderson.[1] The volume of air used was an amount on which the subject, if he were normal, might be expected to reach the limit of this tolerance in about thirty minutes. Respiration rate, blood-pressure and pulse readings were taken for several minutes after the mask was adjusted, but before the actual test was begun. Notes were made on the clinical findings at this time. After the patient began breathing into the apparatus, blood-pressure readings and pulse-rate observations were noted every minute; frequent examinations of the heart were made and the general condition and the color noted.

Although the observers in the Air Service[2] have found psychological tests of extreme importance in the study of the reactions of aviators, the tests described by them were scarcely practicable in individuals of the grade of intelligence found in hospital wards, many of whom are foreigners. We were compelled to resort to simple tests, such as affirmative or negative signs to questions. By

this method we have avoided carrying any of our subjects to complete unconsciousness, but still have been able to test them close to the limit of psychic efficiency, where it manifested itself before physical distress.

In the attempt to obtain sidelights on the efficiency of the subjects studied exercise tests have been carried out usually with a Martin type of bicycle ergometer. Cardiac cases were usually tested with 6000 foot pounds of work in two minutes. Observations were made with respect to any apparent distress or exhaustion, pulse reactions and dyspnea. Air breathed during the exercise and the next minute was collected in a Douglas bag and the quantity expired measured by an experimental gas meter. When the ergometer tests could not be carried out, observations were made on reactions to simple exercises such as stair-climbing.

All gas analyses were made with the well-known Haldane apparatus.

Summary of Cases

Case I.—K. W., white, male, aged forty-five years; coal miner.

Diagnosis. Osteo-arthritis of lumbar spine; second stage pneumokoniosis. The diagnosis of pneumokoniosis was made by *x*-ray. No evidence of cardiovascular disease. Only symptoms were those referable to the osteo-arthritis. Good response to lowered oxygen tension (Chart I).

Case II.—T. H., white, male, aged forty-nine years; potter.

Diagnosis. Pneumokoniosis, second stage; pulmonary emphysema; general vascular sclerosis; chronic constipation. Has been a potter for over thirty years and has had "potter's asthma" for many years. Becomes short of breath on exertion. *X*-ray showed second stage pneumokoniosis. Exercise tolerance fair. Performed work of 6000 foot pounds easily but with more than the usual hyperpnea. Good response to lowered oxygen tension (Chart II).

Case III.—J. N. H., white, male, aged twenty-seven years; laborer.

Diagnosis. Valvular heart disease (aortic stenosis and regurgitation, mitral regurgitation). History of rheumatic fever and repeated attacks of tonsillitis. Shortness of breath on climbing stairs or ladder. Palpitation, especially at night, interfering with sleep. Examination showed slight cyanosis of lips, ears and finger tips; very large heart with transverse measurement of 18 cm. and the signs of advanced disease of the aortic valve, and also mitral involvement. The response to 6000 foot pounds of exercise

in two minutes on the bicycle ergometer was poor. He became exhausted, there was hyperpnea and marked pulse reaction. Fairly good response to lowered oxygen tension (Chart III).

Case IV.—A. O., white, male, aged thirty-two years; blacksmith's helper. Diagnosis. Valvular heart disease (mitral regurgitation); slight decompensation. History of rheumatic fever twelve years ago. Shortness of breath on exertion and palpitation; much worse recently. Cough for five weeks. Examination showed slight cyanosis of lips, ears and finger tips, slight edema of ankles. Transverse measurement of cardiac area 17.5 cm. Moist rales at bases of both lungs. After ten days' rest, cyanosis, rales and edema disappeared. The rebreathing test done at this time showed fairly good response to lowered oxygen tension (Chart IV).

Case V.—J. O. N., white, male, aged forty-nine years; motorman. Diagnosis. Valvular heart disease (mitral stenosis); slight decompensation. Rheumatic fever twenty years ago. Recently, shortness of breath and palpitation on slight exertion; cough worse at night with occasional blood-tinged expectoration, and swelling of feet and legs if he stood much. Examination showed slight orthopnea, transverse cardiac measurement of 16.5 cm., presystolic thrill and murmur. Lungs were somewhat emphysematous, with many moist rales at both bases. The reaction to exercise was poor. He was barely able to do 6000 foot pounds in two minutes on the ergometer. The dyspnea was quite marked but the pulse reaction was not excessive. The response in the rebreathing test was fairly good (Chart V).

Case VI.—M. W., white, female, aged twenty-eight years; housewife. Diagnosis. Valvular heart disease (mitral stenosis). History of attacks of rheumatic fever, nine and seven years ago. For the past three years acute attacks of weakness, shortness of breath and palpitation after exertion; recently had a very severe attack that kept her in bed several days. Examination showed the heart enlarged, with a transverse measurement of 14 cm. Presystolic thrill and murmur, accentuated pulmonic second sound. Few moist rales at bases of both lungs. Pulse-rate unstable, usually normal in the morning, but frequently 100 to 115 in the afternoon. Tolerance to exercise very poor. Dyspnea and marked tachycardia, also a complaint of palpitation on climbing a flight of stairs. The response to lowered oxygen tension was poor (Chart VI).

Case VII.—F. M. B., white, male, aged twenty-seven years; printer. Diagnosis. Valvular heart disease (mitral stenosis); cardiac decompensation. History of scarlet fever and repeated attacks of tonsillitis. Shortness of breath for three years, but three months ago it became so severe that he was unable to walk. Also had vertigo, palpitation and

vertigo. Improved somewhat recently. Examination showed slight cyanosis of ears and finger tips. Heart enlarged; transverse measurement 16 cm. Presystolic thrill and murmur at apex. Many moist rales at the bases of both lungs. Liver extended three finger-breadths below the costal margin in the midclavicular line. Urine contained a cloud of albumin and many casts. Phthalein elimination 37 per cent. in two hours. The reaction to lowered tension of oxygen was poor (Chart VII).

Comment. In view of the comparatively slight respiratory increase that usually occurs in anoxemia, it was to be expected that moderately advanced pneumokoniosis would not interfere very materially with the ability of an individual to compensate for low oxygen. This proved to be the case in two examples of the condition that we tested.

Some of the results in cardiac cases were unexpected. If the heart always played an important part in the compensation for anoxemia, in all the cases presented we should have expected an early breakdown in the rebreathing test. Early failure occurred in two of the five cases—notably in the one with the most advanced decompensation (Case VII). In these two cases, apparently, demands were made on the circulation that could not be met. In the other three cases, particularly in the two with clinical evidences of broken compensation (Cases IV and V), the reserve power of the heart must have been seriously limited. Consequently, the comparatively good runs in the rebreathing test must have been made possible by efficient compensation of the extracardiac mechanisms.

While the rebreathing test may offer a good indication of the general fitness of an individual, the part the circulation plays in any case in the adaptation to anoxemia is particularly difficult to evaluate because there is a coördination of several mechanisms, some of which are known, others doubtless unknown. We have been unable to discover more than a moderate demand for increased cardiac function in cases that we have tested. Moreover we have been unable to demonstrate appreciable enlargement of the heart, either by observations on the position of the apex impulse, or by percussion of the area of cardiac dulness; nor have we observed the marked engorgement of the vessels of the neck that almost invariably accompanies acute dilatation of the right side of the heart.

The variations in response to the anoxemia produced by means of the rebreathing apparatus, among cases with, at most, narrow margins of cardiac reserve, appear to justify the conclusion that the test does not furnish a trustworthy index of circulatory function.

NOTE.—The charts mentioned above will be printed in the *American Journal of the Medical Sciences.*

DISCUSSION

DR. MCKERNON said that these oxygen-want experiments had to be studied with very great care; recently one well-known physiologist died as the result of oxygen want experiments.

DR. L. G. ROWNTREE, of Rochester, Minn., said that in the army, aviators were classified according to the elevation they could stand: 18, 15, or 8 thousand feet; the latter corresponded to the type Dr. Stengel showed on his last two charts. The ability to stand anoxemia had a relation to cardiac disease. One must consider myocardial involvement. There were a number of normal individuals who gave various reactions and the tests should be done with great care. They were very important from a psychological point of view. Some of the patients presented psychological phenomena and symptoms resembling an attack of petit mal, although no evidence of circulatory collapse.

DR. ALFRED STENGEL said these cases were studied from a psychologic standpoint and some experiments were discontinued from the psychological and not the circulatory aspects. This was a valuable method for studying anoxemia, but whether one could pick out the circulatory reactions was doubtful. Some cases with marked myocardial lesions responded the same way as did the controls, so that the cases could not be diagnosed by this means. One patient showed a momentary loss of consciousness.

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